Rising Sun Communications

J11-269140
(unexamined)

CAUTION Post-Edited
Machine Translation

Title of the Invention

Differentiation induction agent

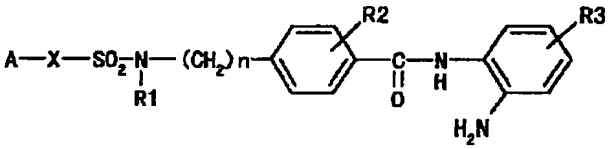
(Abstract) (amended)

(the subject)

It is to put forward novel sulphonamide benzamide derivative having differentiation induction action.

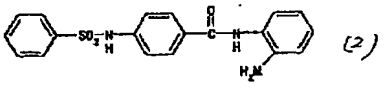
(Method of Solution)

Novel sulphonamide benzamide derivative represented by formula (1).



(1)

For example, the compound represented by formula (2) below is nominated as this sulphonamide benzamide derivative.



(2)

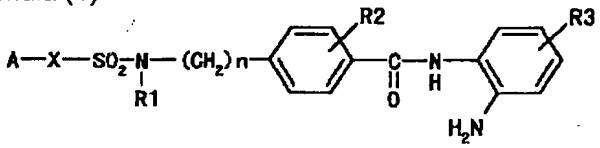
(effect)

Because it has differentiation induction action, it is useful as therapy and/or improvement agent for malignant tumour, autoimmune disease, dermatopathia, parasite infestation.

Patent Claims.

(Claim 1) .

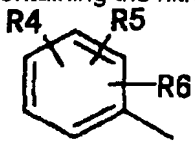
Sulphonamide benzamide derivative or pharmacologically acceptable salt thereof which are represented by formula (1)



(1)

[In the formula, X denotes direct bond, -CH2- group, -CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group, -CH2-CH2-CH2- group, -O-CH2-CH2- group, -CH2-O-CH2-

group, -NR7-CH2-CH2- group, -CH2-NR7-CH2- group, and n denotes 0 or 1, and A denotes one two heteroaromatic ring containing the nitrogen atom which may be substituted or formula (2)

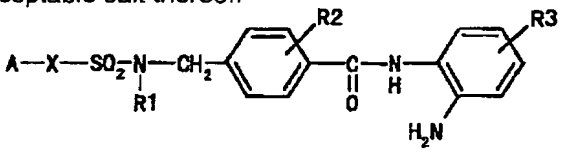


(2)

R1 denotes hydrogen atom, alkyl group of carbon number 1-4, benzyl group, and R2-R6 respectively independently denotes hydrogen atom, halogen atom, amino group, nitro group, hydroxyl group, cyano group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, alkylamino group of carbon number 1-4, dialkylamino group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4 or CO2R1, R7 denotes hydrogen atom, alkyl group of carbon number 1-4, benzyl group, COR1 group, COPh group.]

(Claim 2) .

Sulphonamide benzamide derivative in accordance with Claim 1 represented by formula (3) or pharmacologically acceptable salt thereof.



(3)

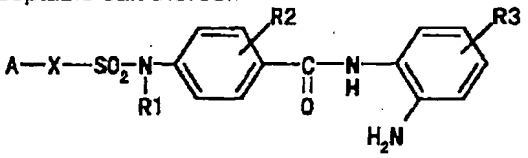
[In the formula, X, A, R1-R3 have the same said meanings.]

(Claim 3) .

Sulphonamide benzamide derivative in accordance with Claim 2 or pharmacologically acceptable salt thereof, wherein A is optionally substituted pyridyl group, and X is direct bond, -CH2- group, -CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group.

(Claim 4) .

Sulphonamide benzamide derivative in accordance with Claim 1 represented by formula (4) or pharmacologically acceptable salt thereof.



(4)

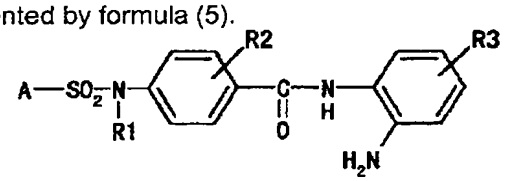
[In the formula A, X, R1-R3 have the same said meanings.)

(Claim 5) .

Sulphonamide benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 4, wherein A is optionally substituted pyridyl group, and X is-CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group, -CH2-CH2-CH2- group, -O-CH2-CH2- group, -CH2-O-CH2- group, -NR7-CH2-CH2- group, -CH2-NR7-CH2- group.

(Claim 6) .

Sulphonamide benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 1 represented by formula (5).

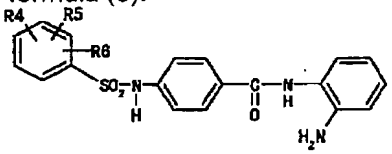


(5)

[In the formula, A, R1-R3 have the same said meanings.]

(Claim 7) .

Sulphonamide benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 1 represented by formula (6).



(6)

[In the formula, R4-R6 have the same said meanings.]

(Claim 8) .

The drug which contains as effective ingredient the compound or pharmacologically acceptable salt thereof in accordance with any of Claims 1-7.

(Claim 9) .

The antitumour agent which contains as effective ingredient the compound or pharmacologically acceptable salt thereof in accordance with any of Claims 1-7.

Detailed Description of the Invention

(0001)

(Technical Sphere of this Invention)

This invention relates to novel sulphonamide benzamide derivative. More particularly the this invention is related to the use as antitumour agent and drug on the basis of differentiation inducing action of novel sulphonamide benzamide derivative.

(0002)

(Technology of the Prior Art)

Presently cancer has overtaken death by cardiac disease and cerebral blood vessel disease, and it is the first place in the diseases as the cause of death. On the other hand, wide ranging study for therapy methods such as surgical operation, radiotherapy, thermotherapy, chemotherapy was performed until now in order to control cancer. Wherein chemotherapy is one of a large pillar of cancer therapy, and many drugs have been found until now, but unfortunately the fully satisfactory drug is not found including side effect until today, and it is the present situation that new drug is waited eagerly for. Many antitumour agents which have been found until now have cancer cell itself as target, and are selected with the aim of killing all the cells which comprise cancer. As mechanism thereof, it acted directly on DNA in a cancer cell and was the one which displayed carcinostatic effect by expressing cell killing effect. However these antitumour agents had poor selectivity of cancer cells to normal cells, consequently it was often the case that side effect expressed in normal cell comprised the limit of treatment.

(0003)

On the other hand, the differentiation induction drug among the antitumour agents has a purpose of inhibiting the property of a cancer cell (infinite proliferation ability) instead of direct cell killing effect, and differentiation is promoted in cancer cells. Various check mechanisms are acted on the differentiated cells, and it is derived to natural death of cell, therefore finally it can lead to proliferation inhibition of a cancer cell and retraction of cancer. In point of retraction of cancer, it is not as much as antitumour agent having cell killing effect because of the mechanism of differentiation inducing action, however, on the other hand, selectivity from the normal cell, low toxicity are expected. Actually, it is known well the retinoic acid which is differentiation induction drug is used with therapy, and high effect is demonstrated in acute promyelocytic leukaemia

(Huang et al.; Blood, vol. 72, 567-572 (1988), Castaign et al., Blood, vol. 76, 1704-1709 (1990), Warrell et al., New Engl. J. Med. vol. 324, 1385-1393 (1991) and the like). Moreover because vitamin D derivative demonstrates differentiation induction action, application to carcinostatic is studied much, too (Olsson et al.; Cancer Res vol. 43, 5862-5867 (1983) and others). These studies are received, and application of vitamin D derivative which is differentiation induction drug (Tokkai 6-179622), isoprene derivative (Tokkai 6-192073), tocopherol (Tokkai 6-256181), quinone derivative (Tokkai 6-305955), non cyclic poly isoprenoid (Tokkai 6-316520), benzoic acid derivative (Tokkai 7-206765), carcinostatic glycolipid (Tokkai 7-258100) have been reported. However there is not a drug which reached sufficient level for cancer curative even by these studies, and an effective drug against various cancers of high safety is desired strongly.

(0004)

Problems to be Overcome by this Invention

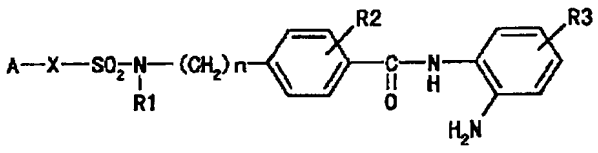
The object of this invention is to put forward a compound having differentiation induction action of cells and useful as drug such as therapy and/or improvement drug for malignant tumour, autoimmune disease, dermatopathia, parasite infestation. The object of this invention is to put forward a novel sulphonamide benzamide derivative or pharmacologically acceptable salt thereof.

(0005)

(Means to Overcome these Problems)

These inventors carried out assiduous investigations to solve these problems, as a result discovered that novel sulphonamide benzamide derivative had differentiation inducing action. This invention was completed as a result of this. In other words, this invention is [1] sulphonamide benzamide derivative or pharmacologically acceptable salt thereof represented by formula (1)

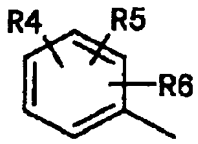
(0006)



(1)

[Wherein X denotes direct bond, -CH2- group, -CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group, -CH2-CH2-CH2- group, -O-CH2-CH2- group, -CH2-O-CH2- group, -NR7-CH2-CH2- group, -CH2-NR7-CH2- group, and n denotes 0 or 1, and A denotes one two heteroaromatic ring containing the nitrogen atom which it may be substituted or formula (2).

(0007)



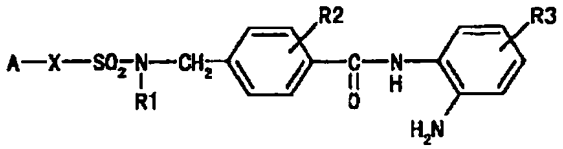
(2)

R1 denotes hydrogen atom, alkyl group of carbon number 1-4, benzyl group, and R2-R6 respectively independently denotes hydrogen atom, halogen atom, amino group, nitro group, hydroxyl group, cyano group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, alkylamino group of carbon number 1-4, dialkylamino group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4 or CO2R1 R 7 denotes hydrogen atom, alkyl group of carbon number 1-4, benzyl group, COR1 group, COPh group.] Moreover.

(0008)

[2] Is sulphonamide benzamide derivative in accordance with [1] represented by formula (3) or pharmacologically acceptable salt thereof, moreover,

(0009)



(3)

[In the formula, X, A, R1-R7 have the same said meanings.]

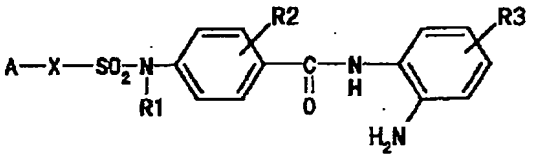
(0010)

[3] sulphonamide benzamide derivative in accordance with [2] or pharmacologically acceptable salt thereof wherein A is optionally substituted pyridyl group, and X is a direct bond, -CH2- group, -CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group, moreover,

(0011)

[4] It is sulphonamide benzamide derivative in accordance with [1] represented by formula (4) (formula 10) and pharmacologically acceptable salt thereof,

(0012)



(4)

[In the formula A, X, R1-R3 have the same said meanings.], moreover,

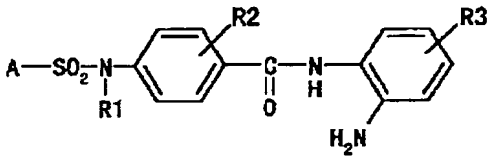
(0013)

[5] It is sulphonamide benzamide derivative in accordance with [4] or pharmacologically acceptable salt thereof, wherein A is optionally substituted pyridyl group, and X is-CH2-CH2- group, -CH=CH- group, -O-CH2- group, -NR7-CH2- group, -CH2-CH2-CH2- group, -O-CH2-CH2- group, -CH2-O-CH2- group, -NR7-CH2-CH2- group, -CH2-NR7-CH2- group, moreover,

(0014)

[6] sulphonamide benzamide derivative in accordance with [1] represented by formula (5) (formula 11) or pharmacologically acceptable salt thereof, moreover,

(0015)



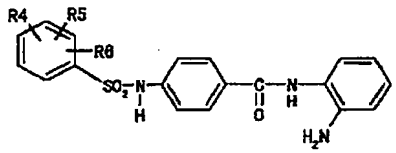
(5)

[In the formula A, X, R1-R3 have the same said meanings]

(0016)

[7] sulphonamide benzamide derivative in accordance with [1] represented by formula (6) (formula 12) or pharmacologically acceptable salt thereof, moreover,

(0017)



(6)

[In the formula, R4-R6 have the same said meanings],

(0018)

[8] drug containing as effective ingredient the compound or pharmacologically acceptable salt thereof in accordance with any of [1]-[7], moreover,

(0019)

[9] antitumour agent containing as effective ingredient the compound or pharmacologically acceptable salt thereof in accordance with any of [1]-[7].

(0020)

Conditions for carrying out this invention

Below, this invention is described in greater detail. As carbon number 1-4 stated in this invention, the carbon number per unit substituent is denoted. In other words, in case of for example dialkyl substitution the carbon number 2-8 is denoted. As halogen atom, fluorine atom, chlorine atom, bromine atom and iodine atom are nominated.

(0021)

As alkyl group of carbon number 1-4, for example methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group are nominated.

(0022)

As alkoxy group of carbon number 1-4, for example methoxy group, ethoxy group, n-propoxy group, isopropoxy group, allyloxy group, n-butoxy group, isobutoxy group, sec-butoxy group, t-butoxy group are nominated. As alkylamino group of carbon number 1-4, for example N-methylamino group, N-ethylamino group, N-iso-propylamino group, N-n-propylamino group, N-n-butylamino group are nominated.

(0023)

As dialkylamino group of carbon number 1-4, there cases wherein alkyl group is the same or different are included, and for example N,N-dimethylamino group, N,N-diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-n-propylamino group, N-ethyl-N-n-propylamino group are nominated. As alkylthio group of carbon number 1-4, methylthio group, ethylthio group, N-propylthio group, N-butylthio group are nominated.

(0024)
As heteroaromatic rings containing one or two nitrogen atoms, for example pyridyl group, pyrimidyl group, pyrazinyl group, pyrrolyl group, imidazolyl group, thiazoyl group, oxazoyl group, quinolyl group, isoquinolyl group are nominated.

(0025)
As a salt of the pharmacologically acceptable compound, salt of inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, orthophosphoric acid and the like which are used regularly in this sphere, and salt of organic acid such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulphonic acid, methanesulphonic acid and the like can be nominated.

(0026)
When the compound of formula (1) has acidic group such as carboxyl group, salt of an alkaline metal such as lithium, sodium, potassium, an alkaline earth metal such as magnesium, calcium, salt of inorganic base such as ammonia or organic base such as methylamine, ethylamine, dimethylamine, trimethylamine, triethylamine, benzylamine can be nominated as salt of the compound, too.

(0027)
As drug, antitumour agent or therapy and/or improvement drug for autoimmune disease, dermatopathia, parasite infestation and the like are nominated. It is 'contained as effective ingredient' is that one or plurality of the compound represented by formula (1) is contained in the formulation. When the compound of formula (1) has asymmetric carbon, all the racemic body thereof, the optically active substances of each are included. Below the representative compound represented with formula (1) of this invention is exemplified using embodiments in table-1 (Table 1-table 30). Moreover this invention is not restricted to these examples.

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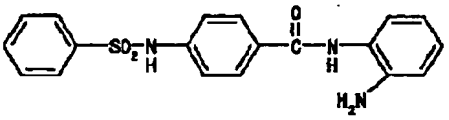
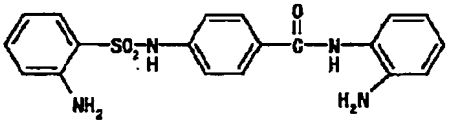
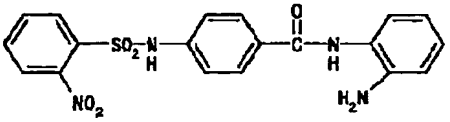
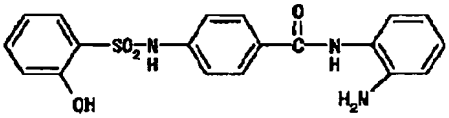
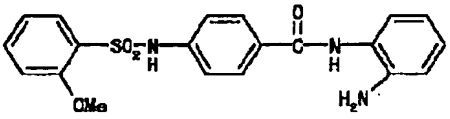
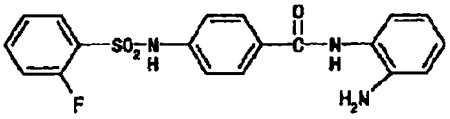
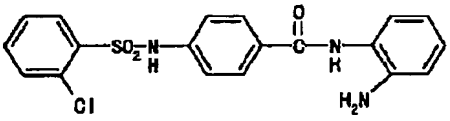
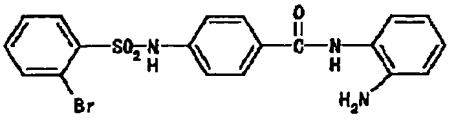
1	
2	
3	
4	
5	
6	
7	
8	

【0029】

【表2】表－1　続きの1

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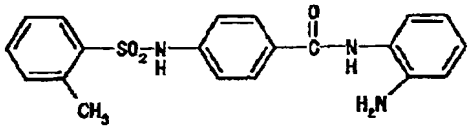

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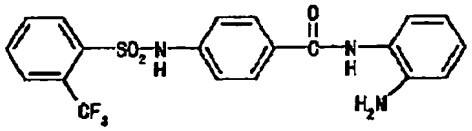

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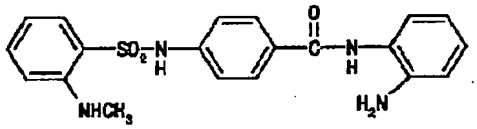

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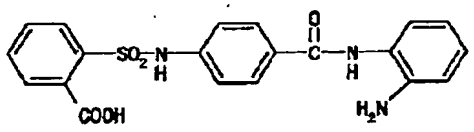

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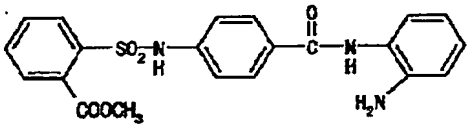

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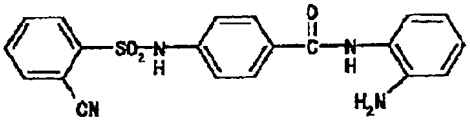

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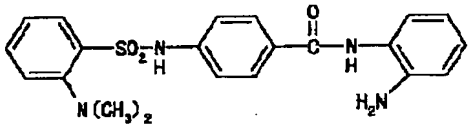

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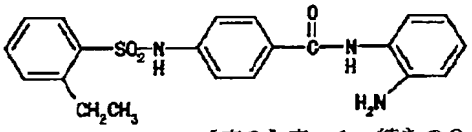
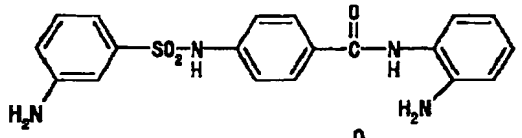
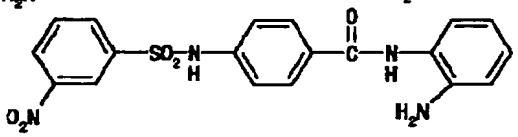
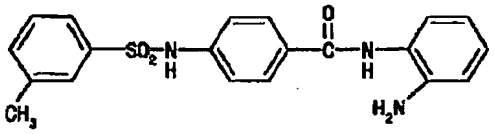


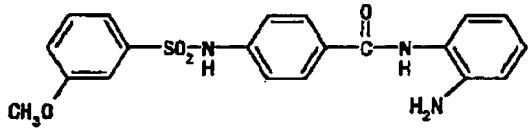
【0030】

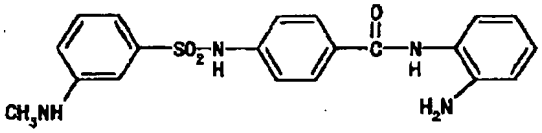
【表3】表－1　続きの2

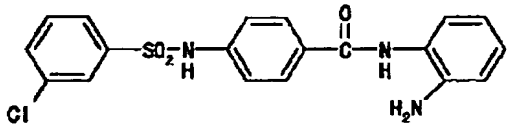
17 

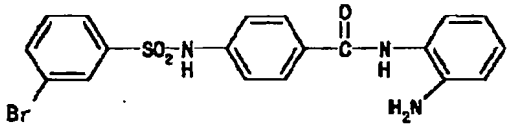
18 

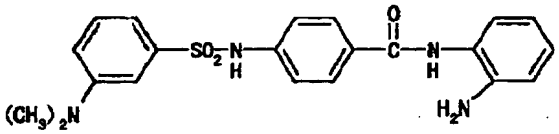
19 

20 

21 

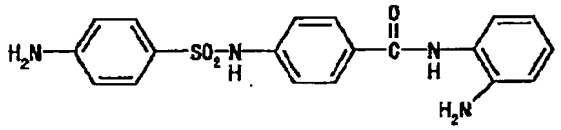
22 

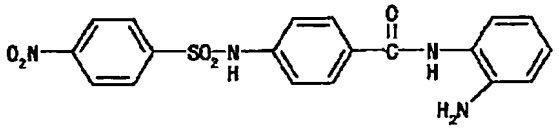
23 

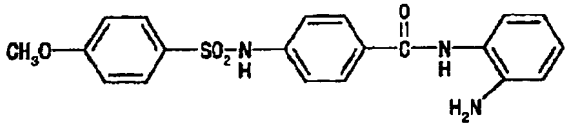
24 

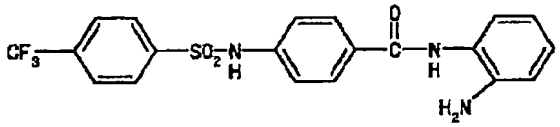
【0031】

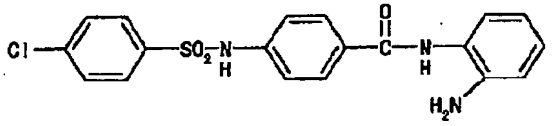
【表4】表－1　続きの3

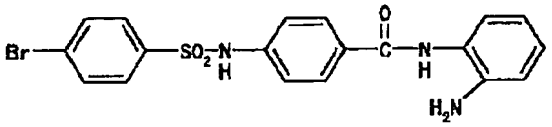
25 

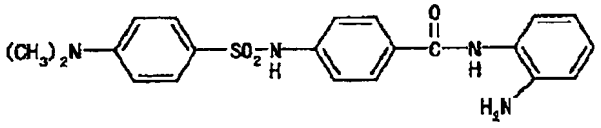
26 

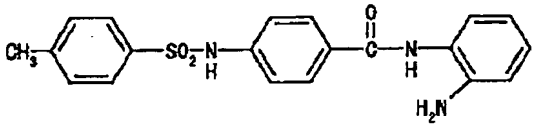
27 

28 

29 

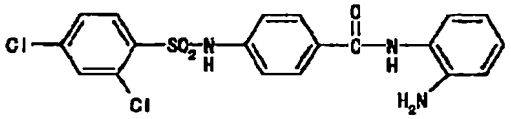
30 

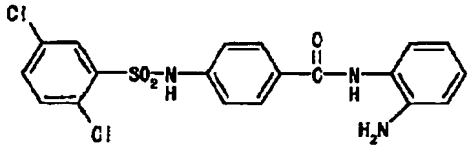
31 

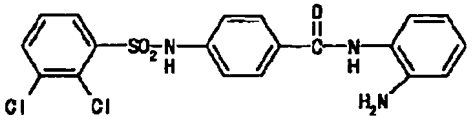
32 

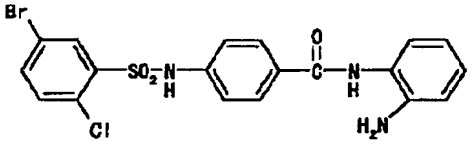
【0032】

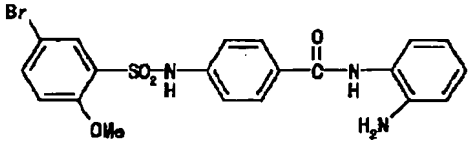
【表5】表－1　続きの4

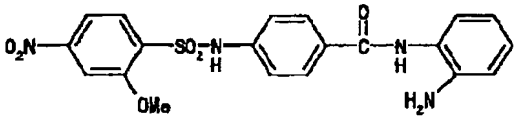
33 

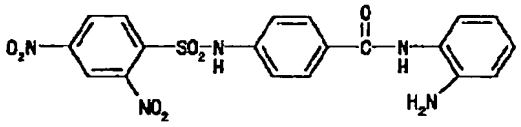
34 

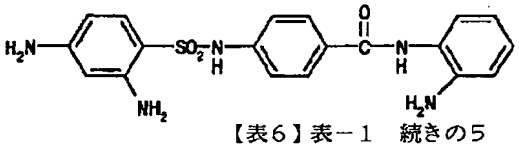
35 

36 

37 

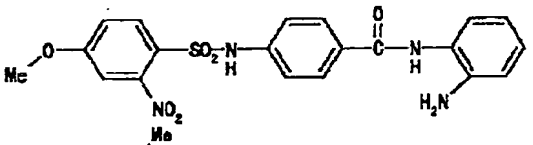
38 

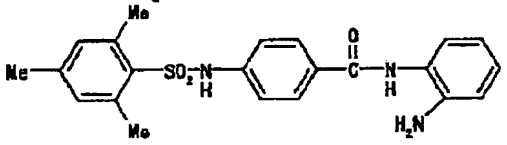
39 

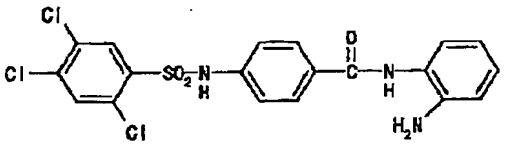
40 

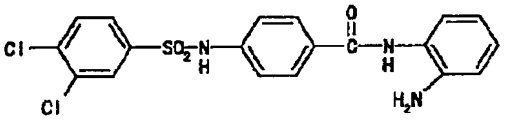
【0033】

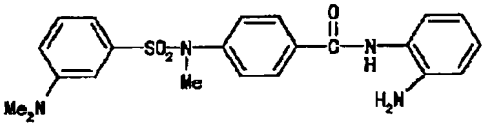
【表6】表－1　続きの5

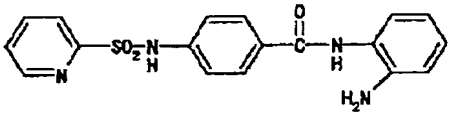
41 

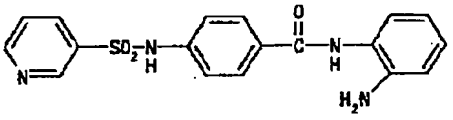
42 

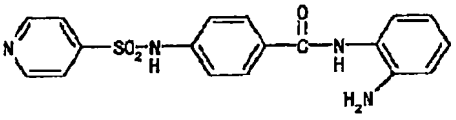
43 

44 

45 

46 

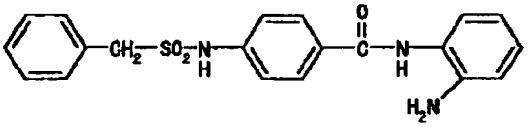
47 

48 

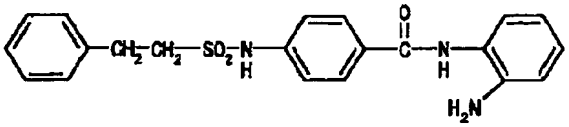
【0034】

【表7】表－1　続きの6

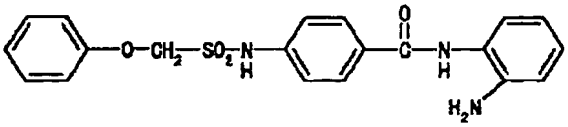
49



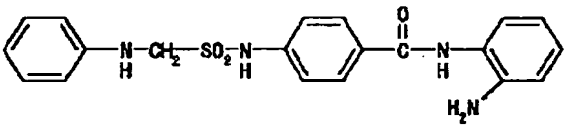
50



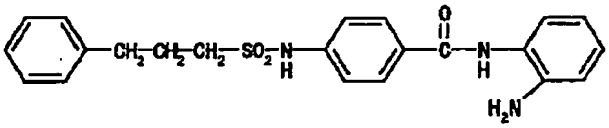
51



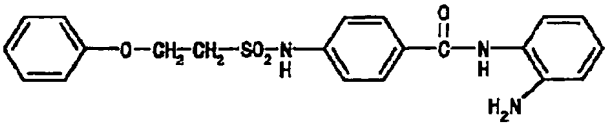
52



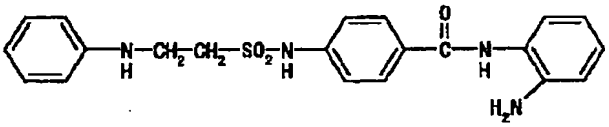
53



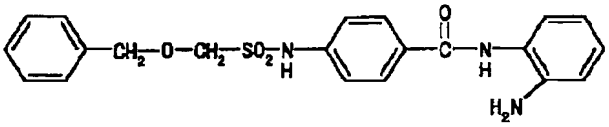
54



55

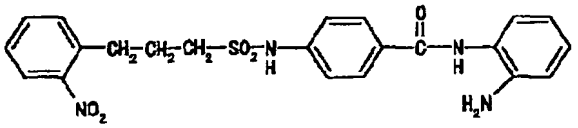


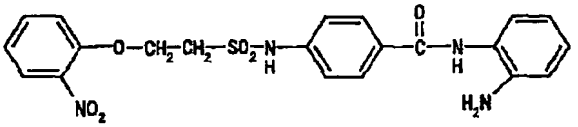
56

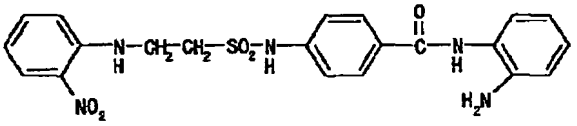


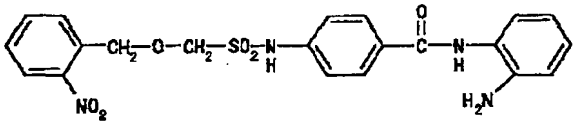
【0035】

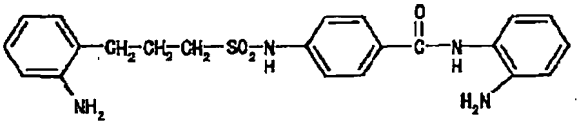
【表8】表－1　続きの7

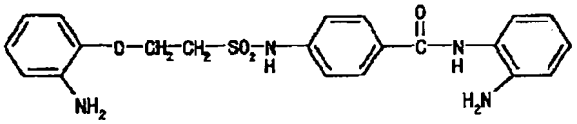
57 

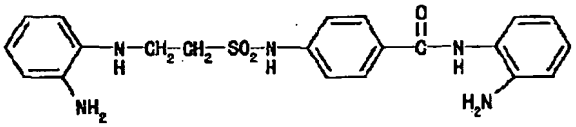
58 

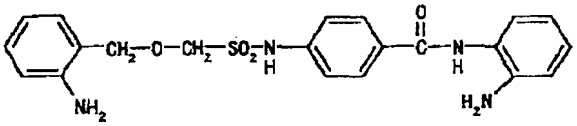
59 

60 

61 

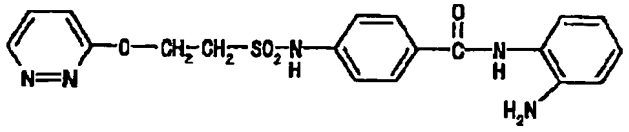
62 

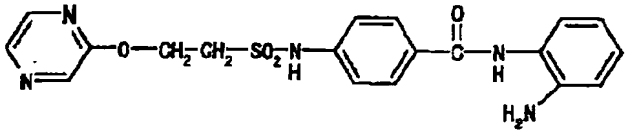
63 

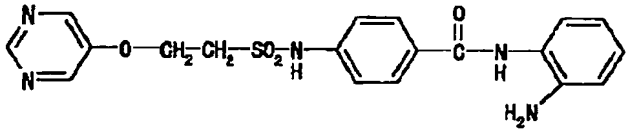
64 

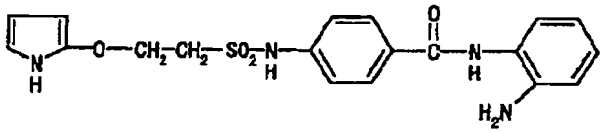
【0036】

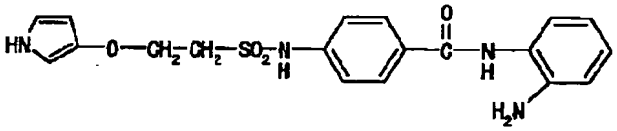
【表9】表－1　続きの8

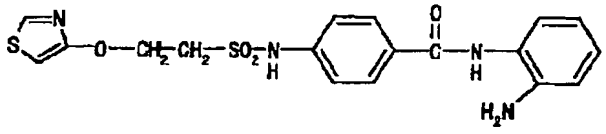
65 

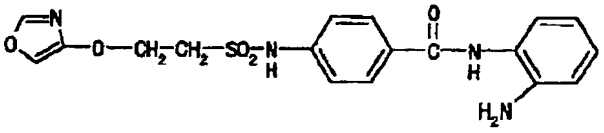
66 

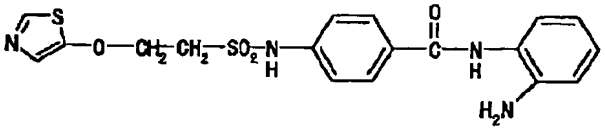
67 

68 

69 

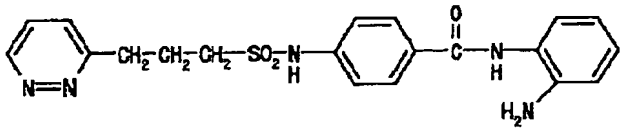
70 

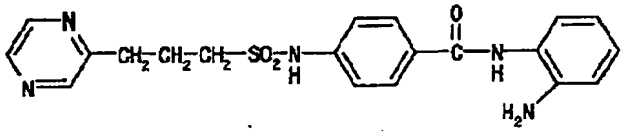
71 

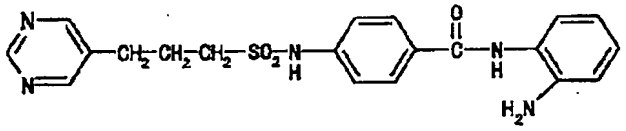
72 

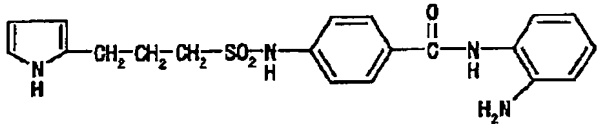
【0037】

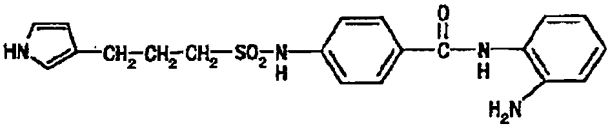
【表10】表－1　続きの9

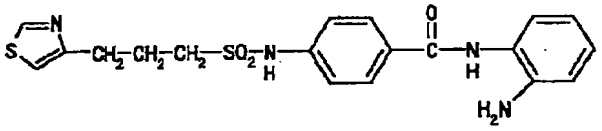
73 

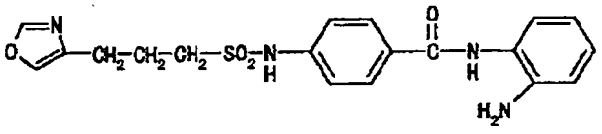
74 

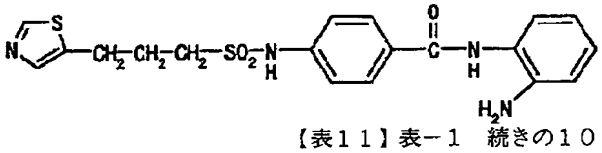
75 

76 

77 

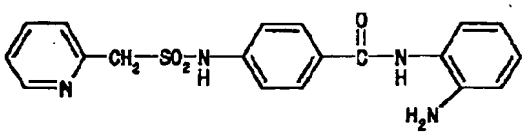
78 

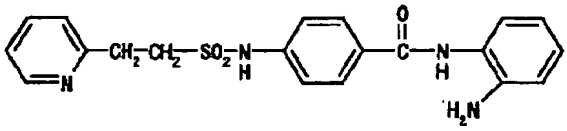
79 

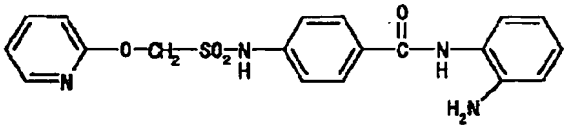
80 

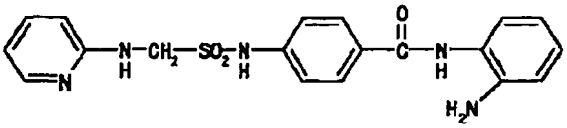
【0038】

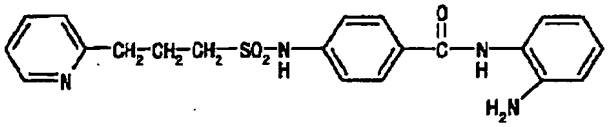
【表11】表－1　続きの10

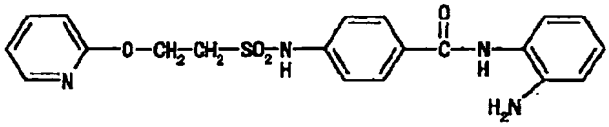
81 

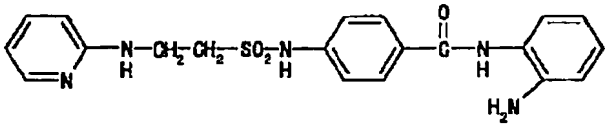
82 

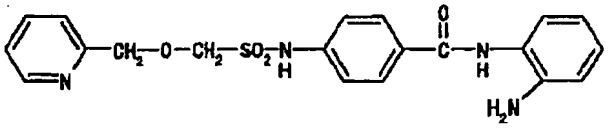
83 

84 

85 

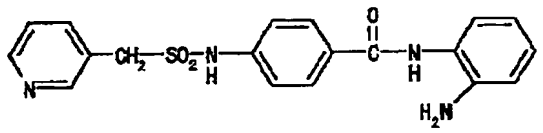
86 

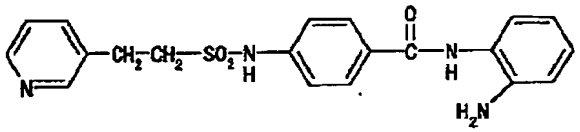
87 

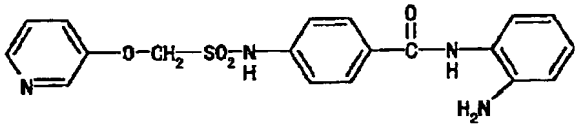
88 

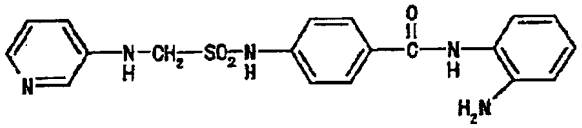
【0039】

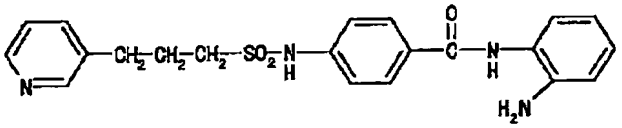
【表12】表－1　続きの11

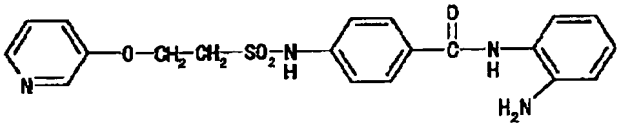
89 

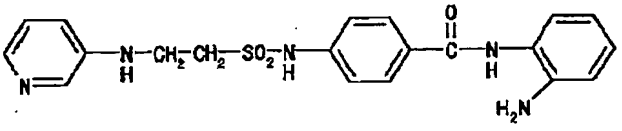
90 

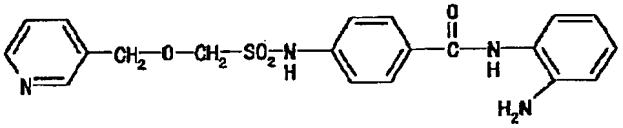
91 

92 

93 

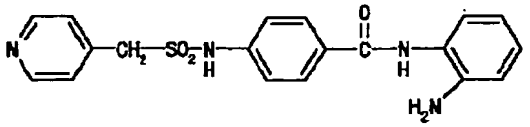
94 

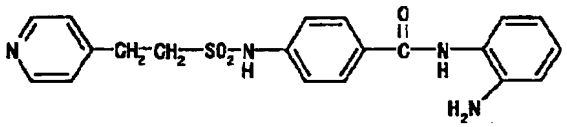
95 

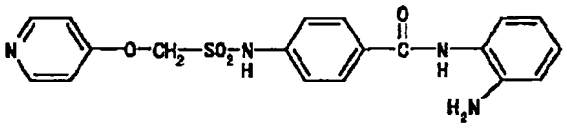
96 

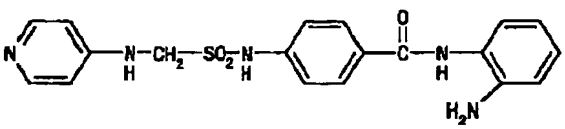
【0040】

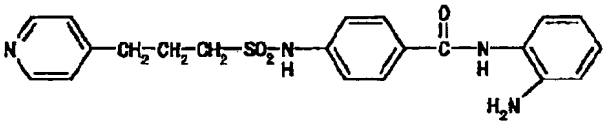
【表13】表－1　続きの12

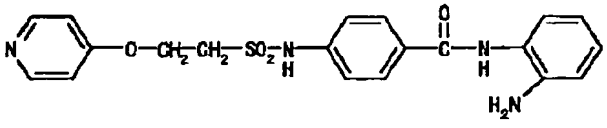
97 

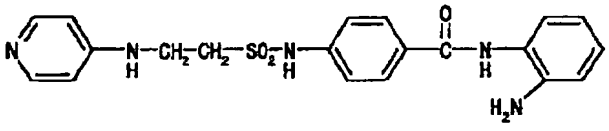
98 

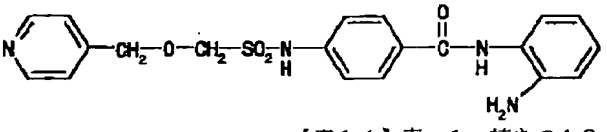
99 

100 

101 

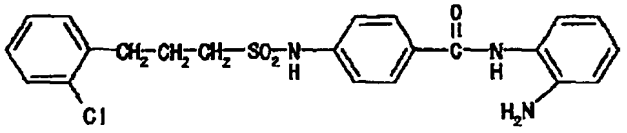
102 

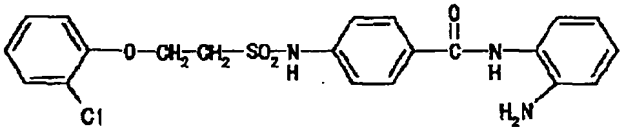
103 

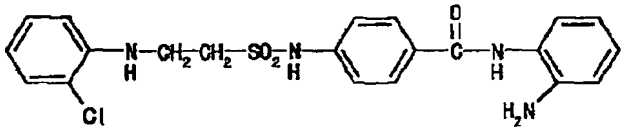
104 

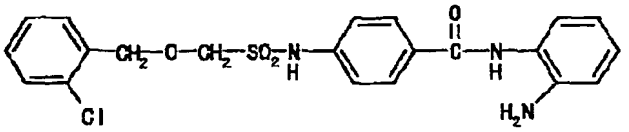
【0041】

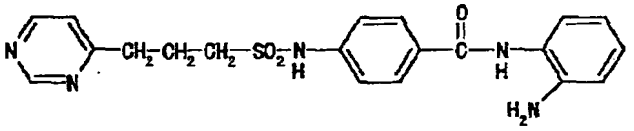
【表14】表－1　続きの13

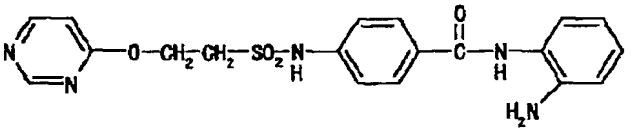
105 

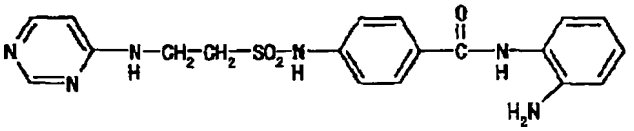
106 

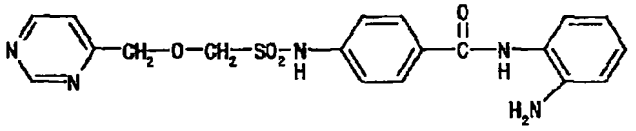
107 

108 

109 

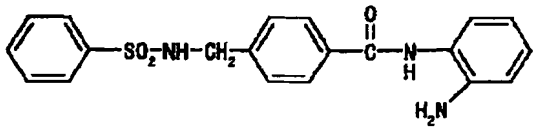
110 

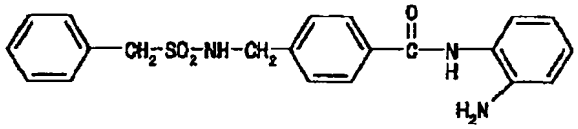
111 

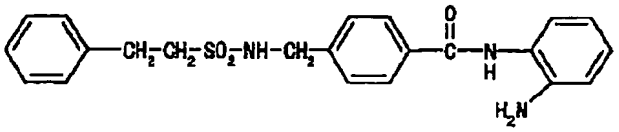
112 

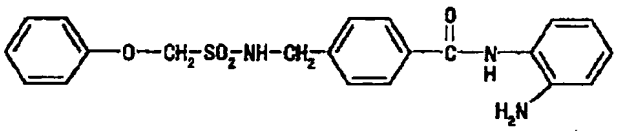
【0042】

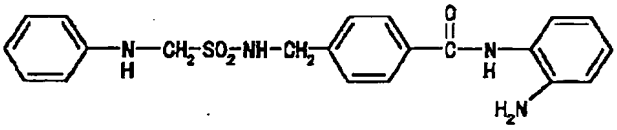
【表15】表－1　続きの14

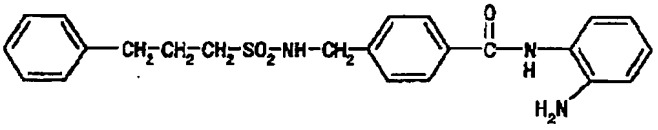
113 

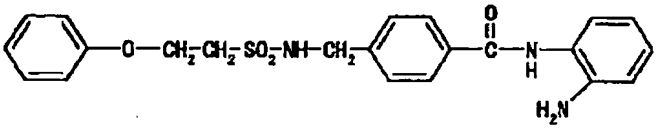
114 

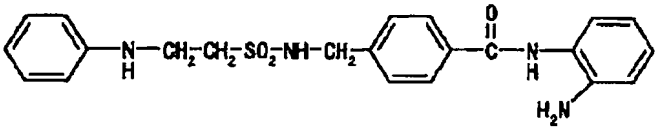
115 

116 

117 

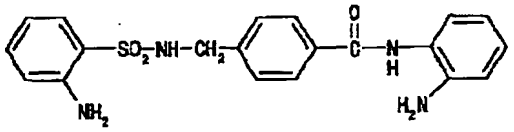
118 

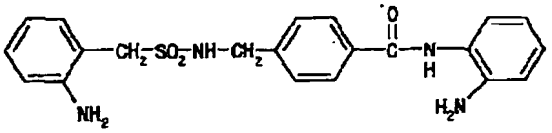
119 

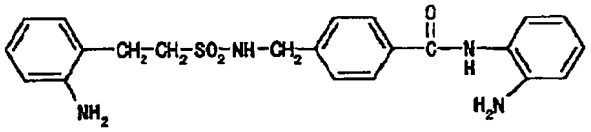
120 

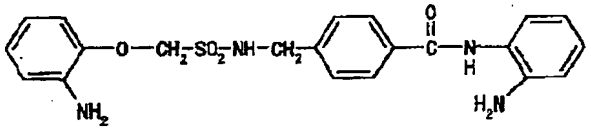
【0043】

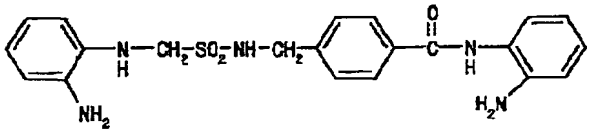
【表16】表－1　続きの15

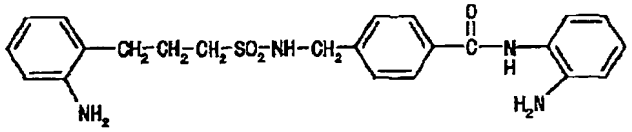
121 

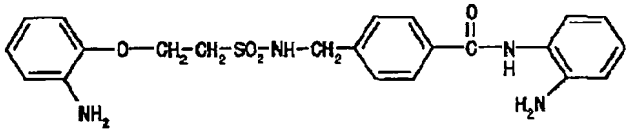
122 

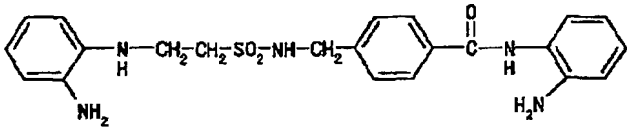
123 

124 

125 

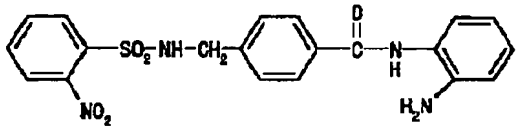
126 

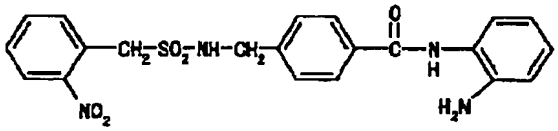
127 

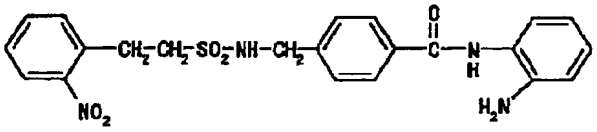
128 

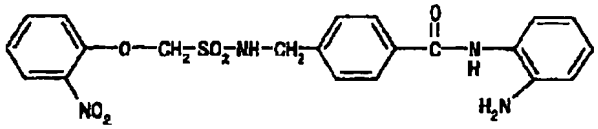
【００４４】

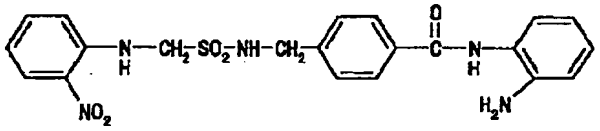
【表１７】表－１　続きの１６

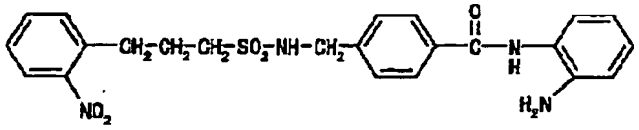
129 

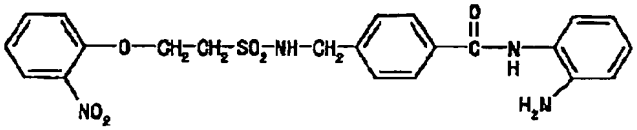
130 

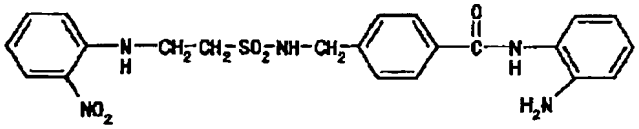
131 

132 

133 

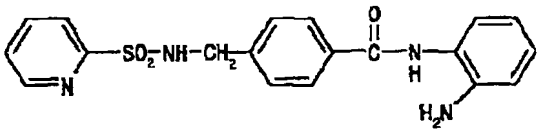
134 

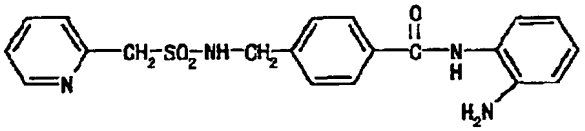
135 

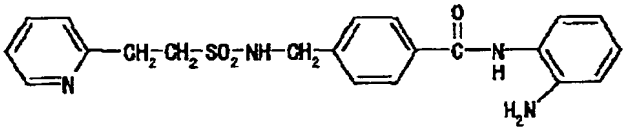
136 

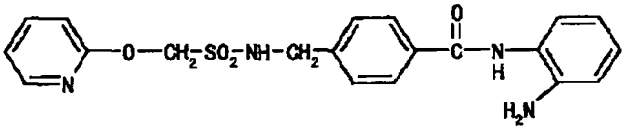
【0045】

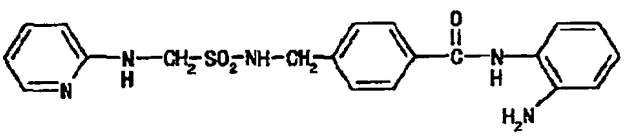
【表18】表－1　続きの17

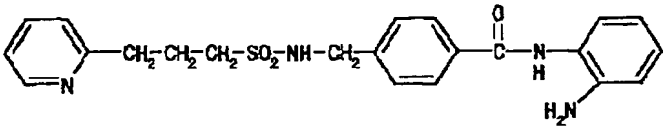
137 

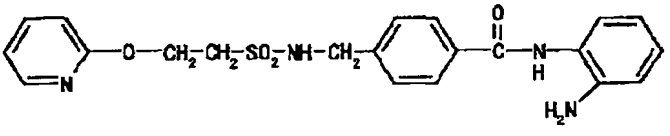
138 

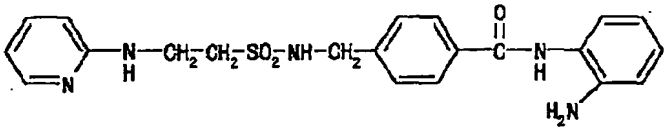
139 

140 

141 

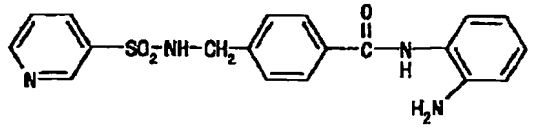
142 

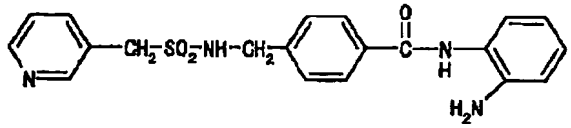
143 

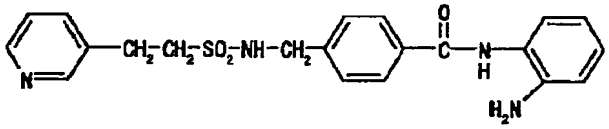
144 

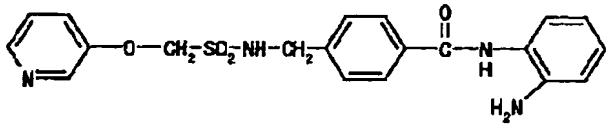
【0046】

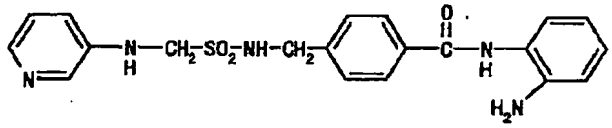
【表19】表－1　続きの18

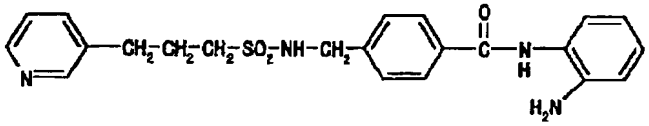
145 

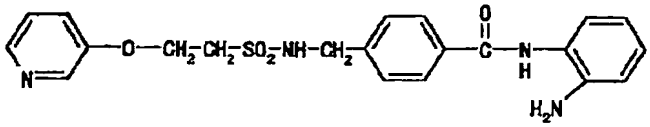
146 

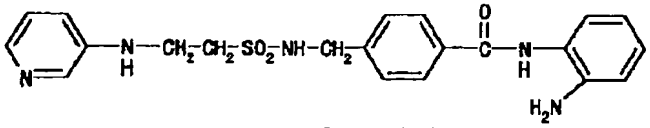
147 

148 

149 

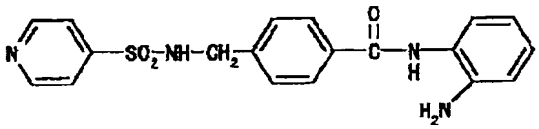
150 

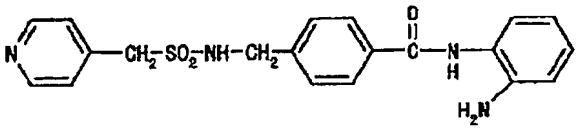
151 

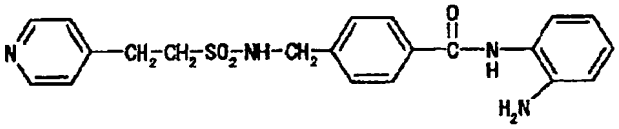
152 

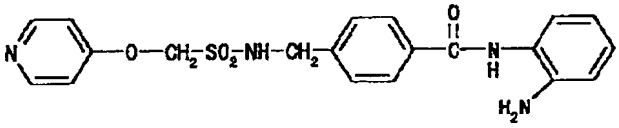
【0047】

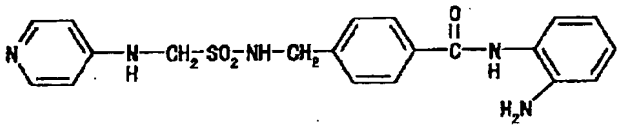
【表20】表－1　続きの19

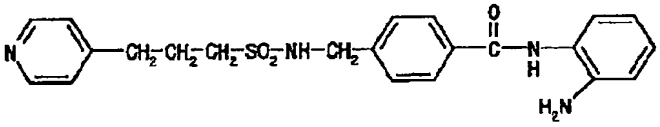
153 

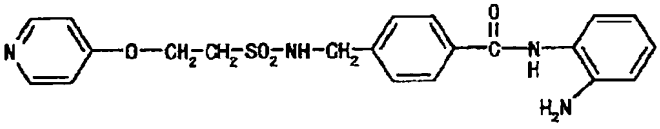
154 

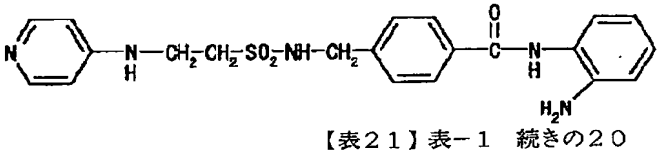
155 

156 

157 

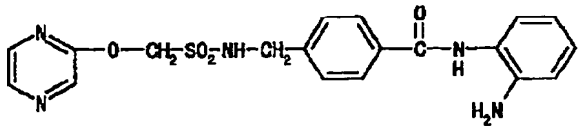
158 

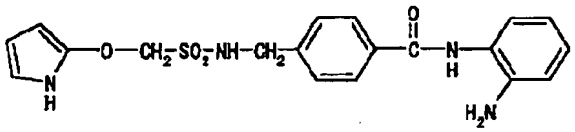
159 

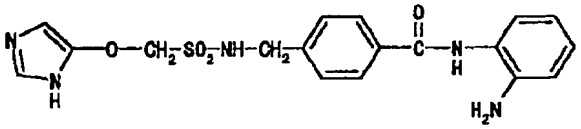
160 

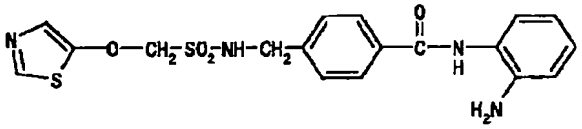
【0048】

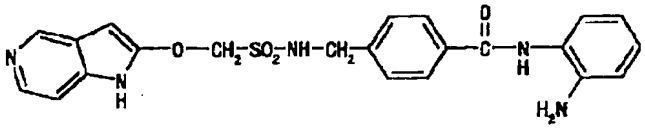
【表21】表－1　続きの20

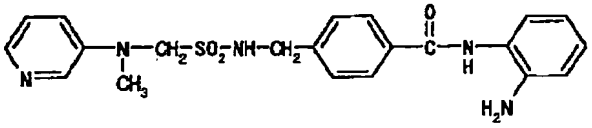
161 

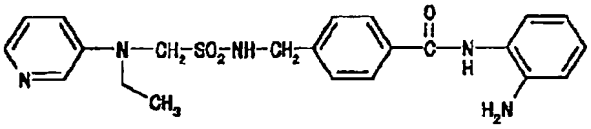
162 

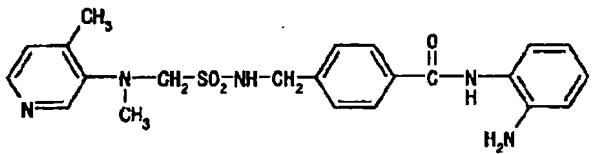
163 

164 

165 

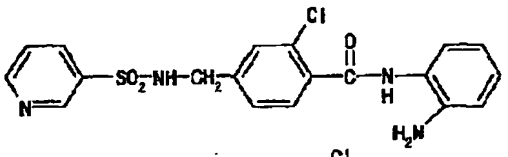
166 

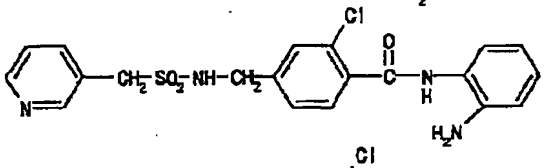
167 

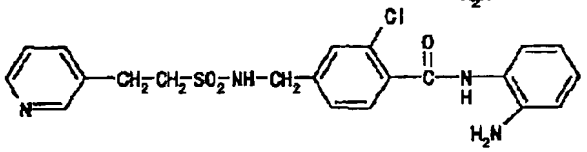
168 

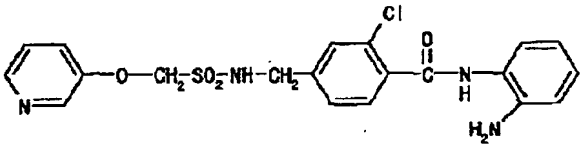
【0049】

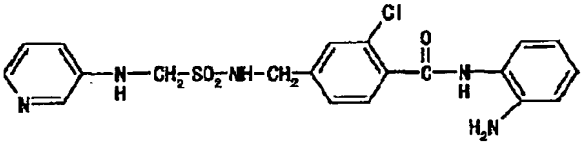
【表22】表－1　続きの21

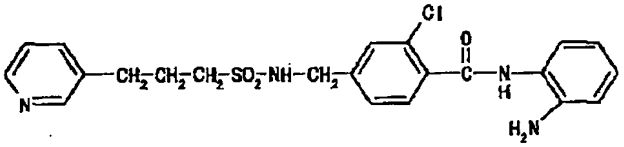
169 

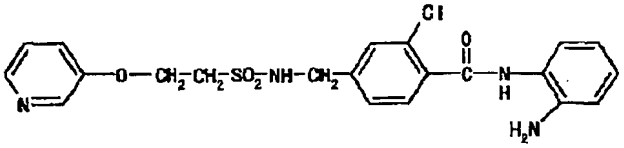
170 

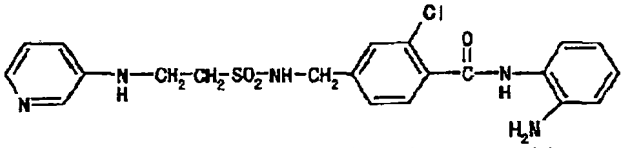
171 

172 

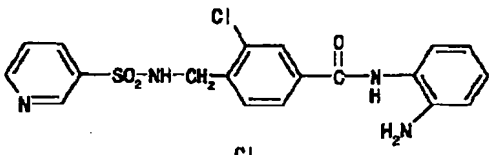
173 

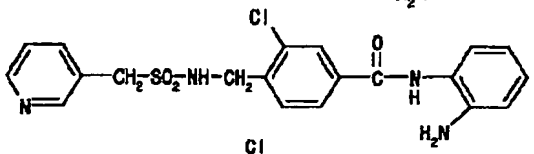
174 

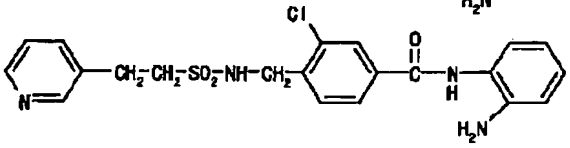
175 

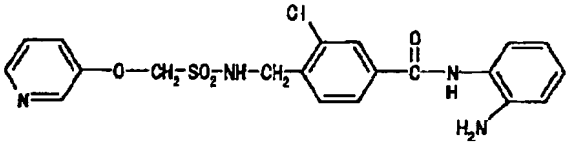
176 

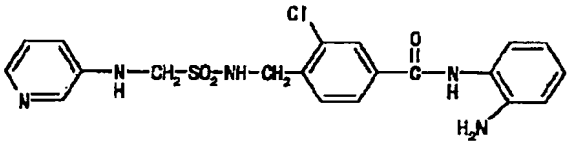
【0050】　　【表23】表－1　続きの22

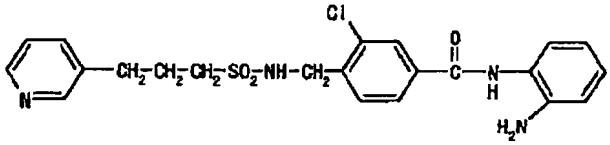
177 

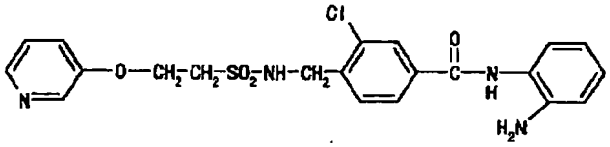
178 

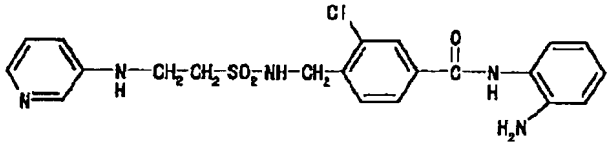
179 

180 

181 

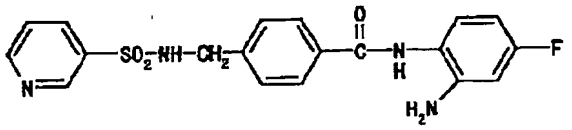
182 

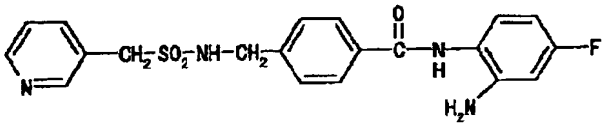
183 

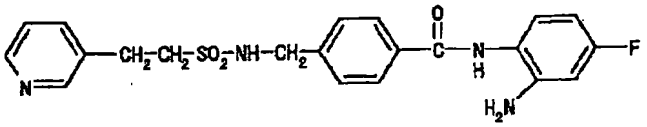
184 

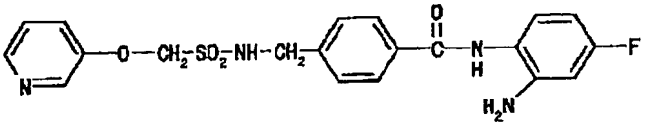
【0051】

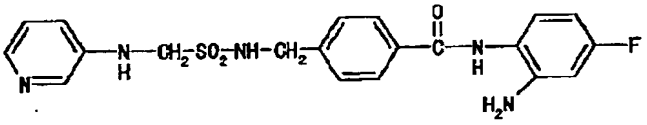
【表24】表－1　続きの23

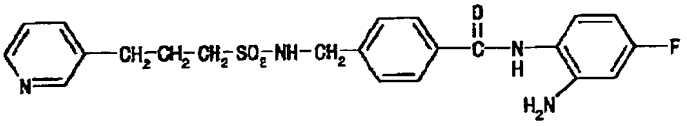
185 

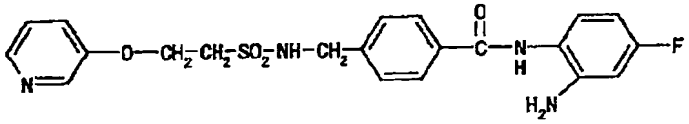
186 

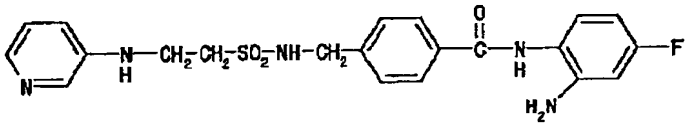
187 

188 

189 

190 

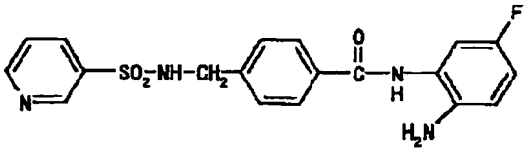
191 

192 

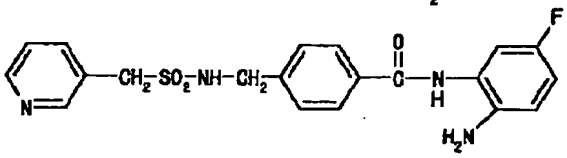
【0052】

【表25】表－1　続きの24

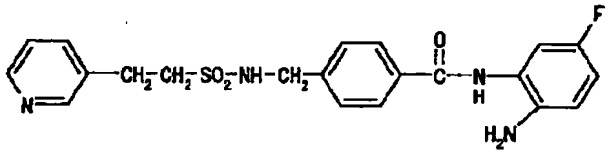
193



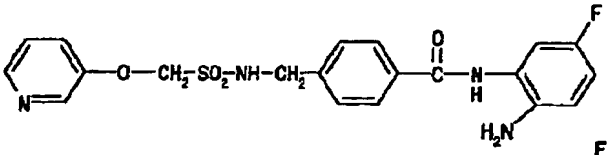
194



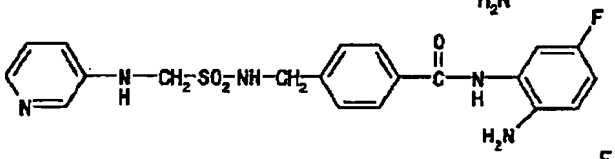
195



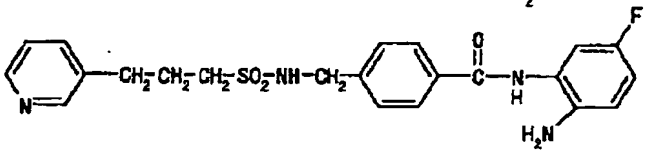
196



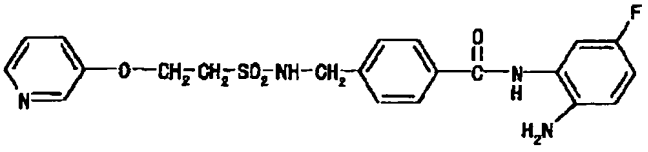
197



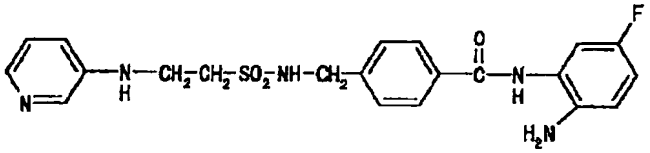
198



199

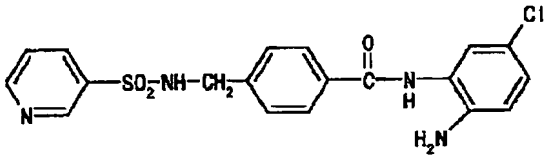


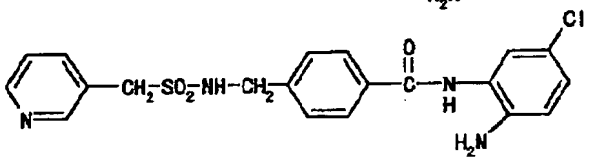
200

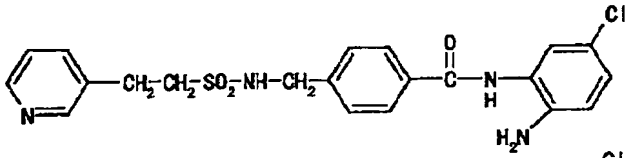


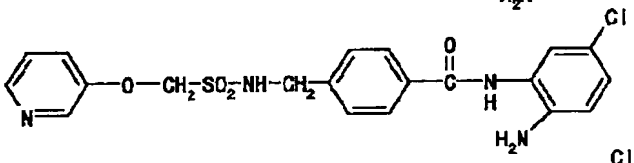
【0053】

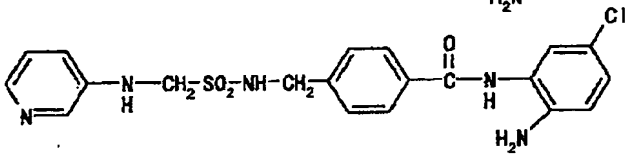
【表26】表－1　続きの25

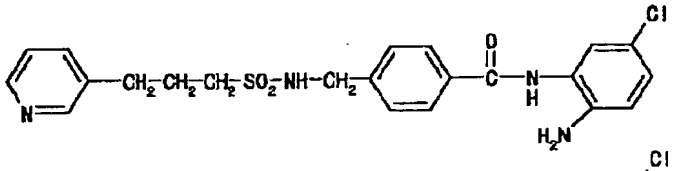
201 

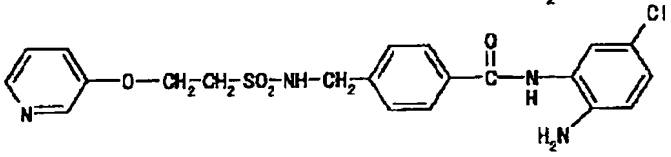
202 

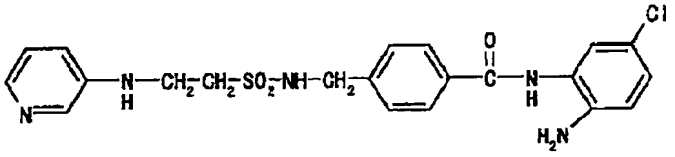
203 

204 

205 

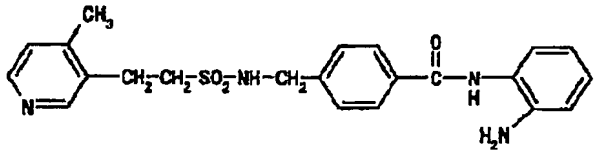
206 

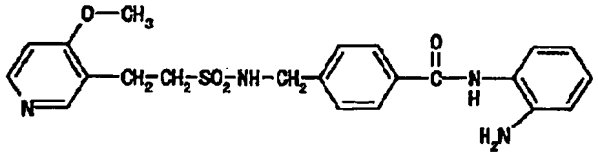
207 

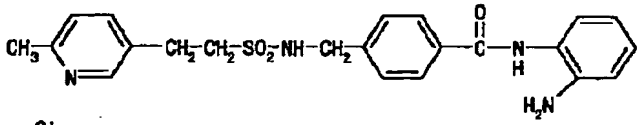
208 

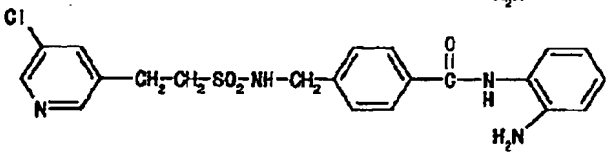
【0054】

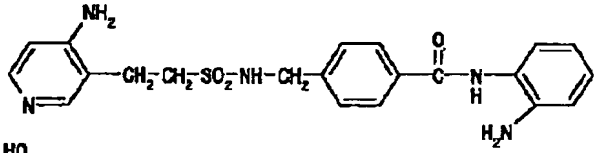
【表27】表－1　続きの26

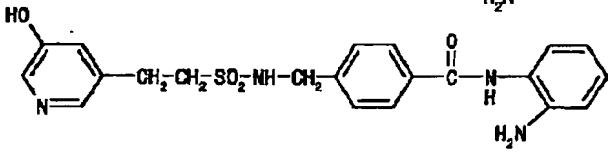
209 

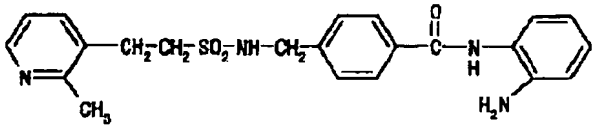
210 

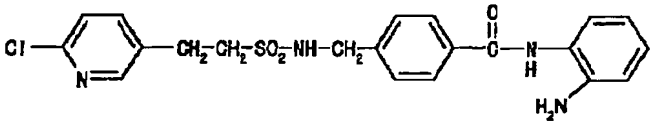
211 

212 

213 

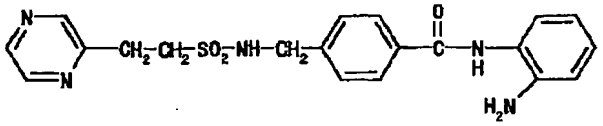
214 

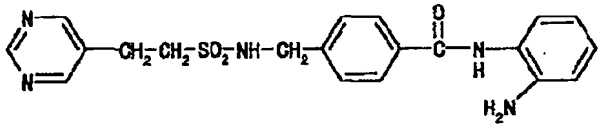
215 

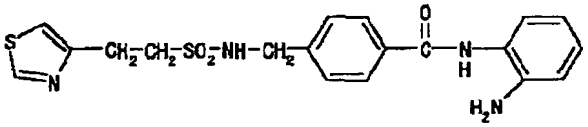
216 

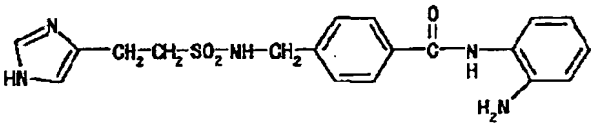
【0055】

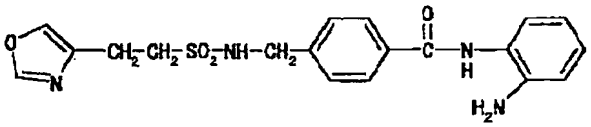
【表28】表－1　続きの27

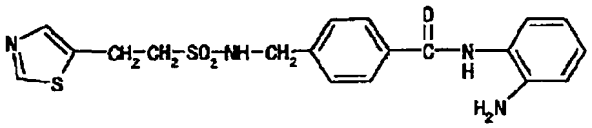
217 

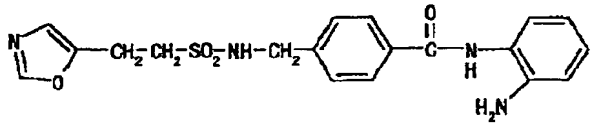
218 

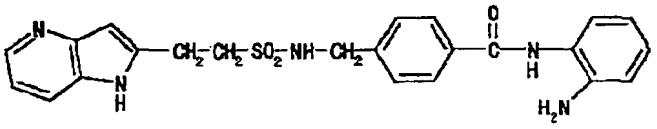
219 

220 

221 

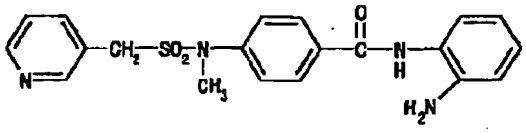
222 

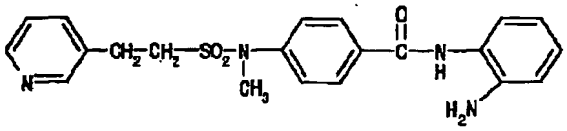
223 

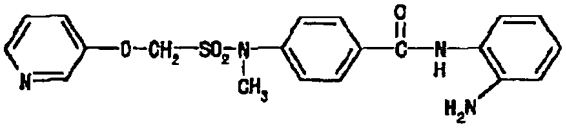
224 

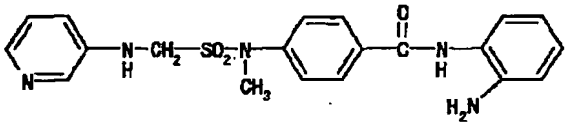
【0056】

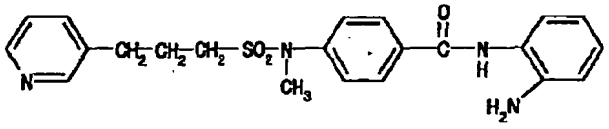
【表29】表－1　続きの28

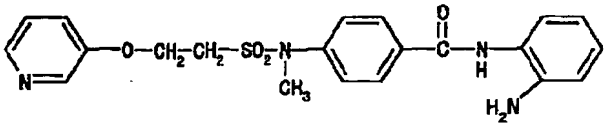
225 

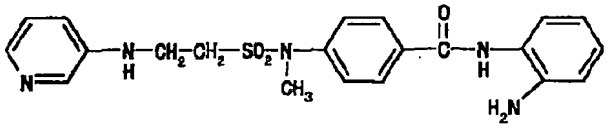
226 

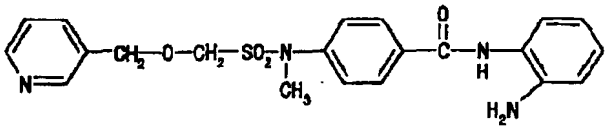
227 

228 

229 

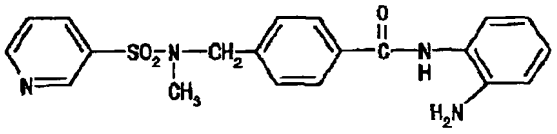
230 

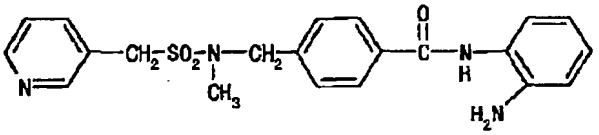
231 

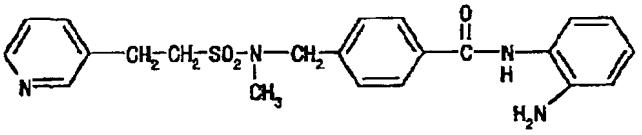
232 

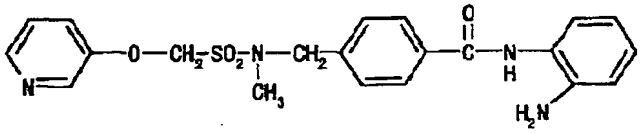
【0057】

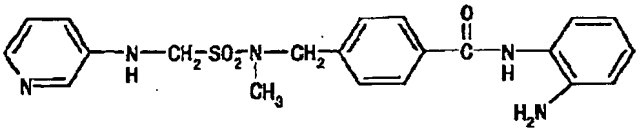
【表30】表－1　続きの29

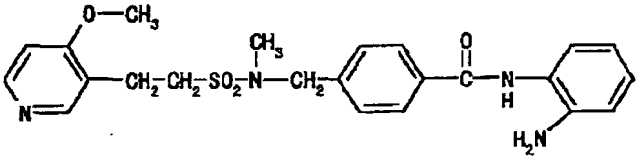
233 

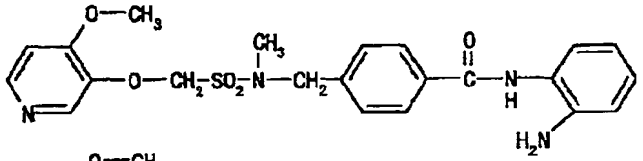
234 

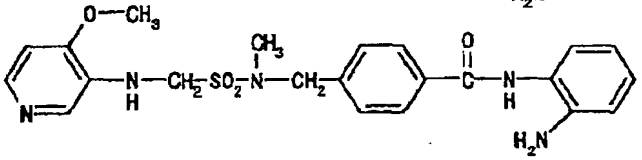
235 

236 

237 

238 

239 

240 

The compound of this invention can be produced for example by the process as follows.

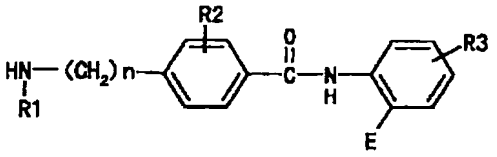
[a] The compound of this invention can be produced by subjecting to condensation reaction the compound represented by formula (7).

(0058)

(7)

[In the formula A, X have the same said meanings. Q denotes hydroxyl group or halogen group] and compound represented by formula (8).

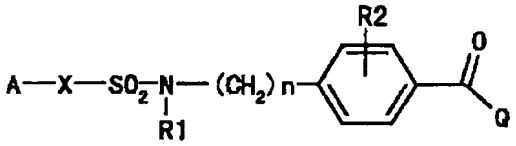
(0059)



(8)

[In the formula, R1, R2, R3, n have the same said meanings. E denotes amino group bonded with protecting group used in conventional peptide synthesis of for example t-butoxycarbonyl group, benzyloxycarbonyl group and the like or nitro group] or [b] by subjecting to condensation reaction the compound represented by compound formula (9).

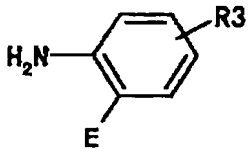
(0060)



(9)

[In the formula, A, X, R1, R2, n, Q have the same said meanings] and the compound represented by compound formula (10).

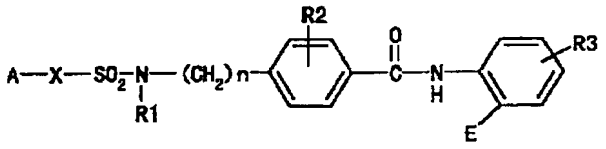
(0061)



(10)

[In the formula, R3, E have the same said meanings], thereby obtained compound represented by formula (11).

(0062)



(11)

[In the formula, A, X, R1, R2, R3, n, E have the same said meanings], is subject to deprotection of protecting group of E or reduction of nitro group.

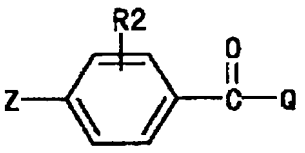
(0063)

The compound represented by formula (7) is marketed or a already known compound which can be readily synthesised, or in the case of novel compound, it can be produced by applying synthesis method of the well known compound reported already. For example, novel sulphonyl chloride can be produced by the process that applied synthesis method described in Chem. Ber., vol. 90, 841 (1957), J. Med. Chem.), vol. 6, 307 (1963), Chem. Lett., 1992, 1483, J. Am. Chem. Soc., vol. 59, 1837 (1937), vol. 78, 2171 (1956).

(0064)

The compound represented by formula (8) is the already known compound, or readily synthesised by subjecting to condensation reaction the compound represented by formula (12).

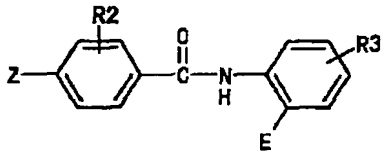
(0065)



(12)

[In the formula formula, Z denotes nitro group or amino group protected with t-butoxycarbonyl group, benzyloxycarbonyl group, trifluoroacetyl group or acetyl group, or aminomethyl group. R2, Q have the same said meanings] and the compound represented by formula (10), thereby obtained compound represented by formula (13).

(0066)



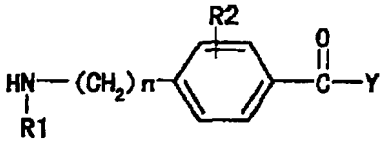
(13)

[In the formula, Z, E, R2, R3 have the same said meanings] is subjected to reduction of nitro group in Z or deprotection of protecting group.

(0067)

The compound represented by formula (9) is the already known compound, which is readily synthesised, or is obtained by subjecting to condensation reaction the compound represented by formula (7) and the compound represented by formula (14).

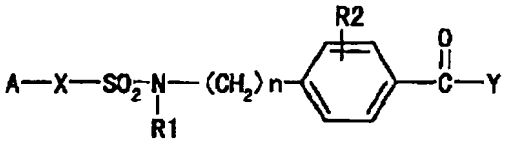
(0068)



(14)

[In the formula formula, R1, R2, n have the same said meanings. Y denotes alkoxy group of carbon number 1-4, benzyloxy group, hydroxy group], thereby obtained compound represented by formula (15).

(0069)



(15)

[In the formula, A, X, R1, R2, Y have the same said meanings] is subjected to deprotection of alkoxy group in Y. The compound represented formula (10) is marketed, or a well known compound which can be readily synthesised or it can be synthesised by process in accordance with later-described Example.

(0070)

Condensation reaction of [a] can be put into effect by process of ordinary sulphonamide bonding reaction of for example acid chloride. For example, when X is hydroxyl group among formula (7), it is reacted with halogenating agent such as phosphorus oxychloride, thionyl chloride, chlorosulphuric acid, phosphorus pentachloride, phosphorus trichloride, oxalyl chloride and the like, and it is converted into acid chloride, thereafter it can be obtained by reacted with the compound represented by formula (8). The reaction is performed in a range of usually -20 degrees to +50 degrees for from 30 minutes to 100 hours. As solvent used, for example, as an aromatic hydrocarbon species such as benzene, toluene, an ether such as tetrahydrofuran, dioxane, ethyl ether and the like, a halogenated hydrocarbon such as dichloromethane, chloroform, N,N-dimethylformamide and a basic solvent of such pyridine, lutidine can be used. By adding organic base, for example, triethylamine or pyridine, 4-(N,N-dimethylamino) pyridine, the reaction rate can be increased.

(0071)
Condensation reaction of [b] can be put into effect by process of amide bond forming reaction, for example active ester or mixed acid anhydride or acid chloride in ordinary peptide. For example, the compound represented by formula (9) and a phenol such as 2,4,5-trichlorophenol, pentachlorophenol, 4-nitrophenol and the like or a N-hydroxy compound such as N-hydroxy succinimide, N-hydroxybenzotriazole and the like are condensed in the presence of dicyclohexylcarbodiimide, and it is converted into active ester and thereafter it is obtained by reacting with the compound represented formula (10).

(0072)
Moreover, the compound represented by formula (9) is reacted with oxalyl chloride, thionyl chloride, phosphorus oxychloride, phosgene, and converted into acid chloride, and thereafter it can be carried out by condensing with the compound represented formula (10). Moreover, mixed acid anhydride is obtained by reacting the compound represented by formula (9) with methyl chlorocarbonate ester, chlorocarbonic acid ethyl ester, chlorocarbonic acid benzyl, chlorocarbonic acid isobutyl, methanesulphonyl chloride, anhydrous trifluoroacetic acid and next it can be obtained by being condensed with the compound represented formula (10).

(0073)

Furthermore, aforesaid condensation reaction can be carried out by using peptide condensation reagent alone such as dicyclohexylcarbodiimide, N,N-carbonyldiimidazole, diphenyl phosphoric acid azide, cyano phosphoric acid diethyl, 2-chloro-N,N'-dimethyl imidazolinium chloride and the like.

(0074)
The reaction is carried out at -20 to +50 degrees usually for 30 minutes to 100 hours. As the solvent used, for example, an aromatic hydrocarbon species such as benzene, toluene, an ether such as tetrahydrofuran, dioxane, ethyl ether and the like, a halogenated hydrocarbons such as dichloromethane, chloroform, or N,N-dimethylformamide and an alcohol such as ethanol and methanol and the like, organic base such as pyridine, lutidine or mixture thereof are nominated. By adding organic base for example triethylamine or pyridine, 4-(N,N-dimethylamino) pyridine, the reaction rate can be increased.

(0075)
The compound represented by formula (1) can easily form salt with pharmacologically acceptable acid. As acid thereof, in addition to an inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, orthophosphoric acid used regularly in this sphere, an organic acid such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulphonic acid, methanesulphonic acid are nominated. These salts can also be used as the effective ingredient compound of this invention in the same way as in the molecular form of the compound of formula (1). The compound represented by formula (1) can be isolated and purified from the reaction mixture by ordinary separation means, for example process such as extraction, recrystallisation method, column chromatography.

(0076)
Novel benzamides of this invention have differentiation induction action and are useful as therapy and/or improvement agent for malignant tumour, autoimmune disease, dermatopathia, parasite infestation. Wherein, as malignant tumour, in addition to hematopoietic organ tumours such as acute leukaemia, chronic leukaemia, malignancy lymphoma, multiple myeloma, macroglobulinemia, solid tumours such as colon cancer, brain tumour, head cervix cancer, breast cancer, lung cancer, cancer of the esophagus, gastric cancer, hepatoma, gallbladder cancer, bile duct cancer, pancreatic carcinoma, insula pancreatica cell cancer, kidney cell cancer, adrenal cortex cancer,

tumour of the urinary bladder, prostatic cancer, testis tumour, ovary cancer, uterine cancer, carcinoma villosum, cancer of the thyroid, bad carcinoid tumour, skin cancer, malignant melanoma, osteosarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumour, retinoblastoma are nominated.

(0077)
As autoimmune disease, rheumatism, nephritis, diabetes mellitus, systemic lupus erythematosus, human autoimmune lymphocytotic lymphadenopathy, immunoblastic lymphadenopathy, Crohn's disease, ulcerative colitis are nominated.

(0078)
As dermatopathia, psoriasis, acne, eczema, atopic dermatitis, parasitic dermatosis, alopecia, pyogenic dermatosis, skin sclerosis are nominated. As parasite infestation, a disease caused by infection of parasite such as malaria infection is denoted. Moreover target disease of this invention does not need to be restricted to these.

(0079)
The effective ingredient compounds of this invention are useful as drug, and these are used in a form of general medical formulation. Formulation is prepared using diluent of for example filler, expander, binding agent, moisturising agent, disintegrating agent, surface active agent, lubricant or excipient which are usually used. As this drug formulation, various forms can be selected corresponding to the therapy object and as representative thereof, tablet, pill, powder, liquid medicine, suspending agent, emulsion, granule, capsule agent, injection (liquid medicine, suspending agent) and suppository and the like are nominated.

(0080)
When it is formed into a tablet, various ones which is known well in the prior art as a carrier in this sphere, can be widely used. As example thereof, for example excipient such as lactose, dextrose, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and the like, binding agent such as water, ethanol, propyl alcohol, single syrup, dextrose liquid, starch liquid, gelatine solution, carboxymethyl cellulose, shellac, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as dried starch, sodium alginate, agar powder, carmellose calcium, starch, lactose, disintegration depressant such as refined sugar, cacao butter, hydrogenation oil, absorption promoter such as quaternary ammonium salt group, sodium lauryl sulphate and the

like, moisturising agent such as glycerine, starch and the like, adsorbent such as starch, lactose, kaolin, bentonite, colloidal silicic acid, lubricant such as talc, stearate, polyethyleneglycol and the like can be used. Furthermore, as for a tablet, it can be made into coated tablet of ordinary agent in accordance with requirements, for example sugar coated tablet, gelatine encapsulation tablet, enteric-coated encapsulation tablet, film coating tablet or bilayer tablet, multilayer tablet.

(0081)
When it is formed into pill, ones well known in prior art in this sphere as a carrier, can be widely used. As example thereof, for example excipients such as crystalline cellulose, lactose, starch, hardening vegetable oil, kaolin, talc and the like, binding agent such as powdered gum Arabic, tragacanth powder, gelatine and the like, disintegrating agent such as carmellose calcium, agar and the like are nominated. Capsule agent is prepared by mixing the effective ingredient compound with above-mentioned various carriers according to conventional method, and packing into hard gelatine capsule, soft capsule and the like.

(0082)
When it is prepared as injection, it is preferred that liquid medicine, emulsion and suspending agent are sterilised and are isotonic with blood, and when it is formed into these, ones conventionally used in prior art in this sphere as diluent, for example water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species can be used. In this case, sodium chloride, dextrose or glycerine of necessary quantity may be contained in drug formulation to prepare an isotonic solution, and moreover ordinary solubiliser, buffer agent, analgesic and the like may be added.

(0083)
When it is formed into suppository, ones well known in prior art as a carrier can be widely used. As example thereof, for example semi-synthetic glyceride, cacao butter, esters of higher alcohol, higher alcohol, polyethyleneglycol and the like are nominated. Furthermore colorant, preservative, flavour, flavour agent, sweetener and other drug can be contained in the drug formulation in accordance with requirements. The quantity of the effective ingredient compound which should be contained in these drug formulations of this invention is not restricted in particular and suitably selected from a wide range, but it is usually about 1-70 wt.% and preferably made into about 5-50 wt.% in the formulation composition.

(0084)

As for the administration method of these drug formulation of this invention, there are no restrictions in particular and it is administered by the methods that suits various formulation, age of patient, sex, degree of disease and other conditions. For example, in the cases of tablet, pill, liquid medicine, suspending agent, emulsion, granule and capsule agent, it is orally-administered, and in the case of injection, it is administered intravenously by itself or by being mixed with ordinary fluid replacement such as glucose, amino acid, and furthermore it is administered intramuscularly, subcutaneously or intraperitoneously by itself in accordance with requirements. In the case of suppository, it is administered in rectum.

(0085)

Dosage of these drug formulation of this invention is suitably selected by application, age of patient, sex, degree of disease and other conditions, but it is usually made into about around 0.0001-100 mg as the quantity of the effective ingredient compound per day per 1 kg weight. Moreover, it is desirable that the effective ingredient compound is contained by about 0.001-1,000 mg range in the formulation of administration unit form. The compound and salts thereof represented by formula (1) of this invention do not demonstrate toxicity in dosage that demonstrates pharmacological effect.

(0086)

(Example)

Below this invention is described in greater detail with Examples and pharmacological test example, but this invention is not restricted to these. Moreover number in brackets of title is the number of the compound exemplified in Detailed Description.

(0087)

Example 1.

Synthesis of N-(2-amino) phenyl-4-benzensulphonyl amino benzamide (Table 1, compound number 1).

(1-1) Water (500 ml) solution of sodium hydroxide 22 g (550 mmol) was added into dioxane (1000 ml) solution of o-phenylenediamine 54.0 g (500 mmol), and dioxane (500 ml) solution of di tert-

butyl di carbonate 109.1 g (550 mmol) was added under ice cooling. It was stirred at room temperature for six hours, thereafter left to stand at room temperature overnight. The solvent was concentrated to 1/2 vol and next, was extracted with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and next it was dried, the solvent was eliminated by distillation, and the obtained residue was refined by silica gel column chromatography (chloroform), and obtained solid was washed with ethyl ether, thereby N-tert-butoxycarbonyl-o-phenylenediamine 34.2 g (yield 33 %) were obtained as white solid.

1H NMR (270 MHz, CDCl3) delta ppm: 1.51 (9H, s), 3.75 (2H, s), 6.26 (1H, s), 6.77 (1H, d, J = 8.1 Hz), 6.79 (1H, dd, J = 7.3, 8.1 Hz), 7.00 (1H, dd, J = 7.3, 8.1 Hz), 7.27 (1H, d, J = 8.1 Hz).

(0088)

(1-2) .

Triethylamine (21 ml, 150 mmol) was added to dichloromethane (300 ml) solution of compound 20.8 g obtained with step (1-1) (100 mmol), and furthermore dichloromethane (100 ml) solution of 4-nitrobenzoyl chloride 20.0 g (108 mmol) was gradually added under ice cooling and thereafter was stirred for seven hours. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with chloroform. Organic layer was washed with 1 N hydrochloric acid aqueous solution, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and next, it was dried, and the solvent was eliminated by distillation. By washing obtained residue with diisopropyl ether, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-nitrobenzamide 35.1 g (yield 98 %) were obtained as the straw-coloured solid.

1H NMR (270 MHz, CDCl3) delta ppm: 1.53 (9H, s), 7.17-7.29 (4H, m), 7.85 (1H, brd, J = 7.3 Hz), 8.17 (2H, d, J = 8.8 Hz), 8.32 (2H, d, J = 8.8 Hz), 9.88 (1H, brs).

(0089)

(1-3) .

10 % palladium carbon (50 % wet., 2.5 g) was added under a stream of nitrogen to THF (200 ml)-methanol (200 ml) mixed solution of compound 10.0 g (28.0 mmol) obtained with Step (1-2) and was stirred for one hour 30 minutes under a stream of hydrogen. Absorption of hydrogen stopped, and next, catalyst was separated by filtration, and the solvent was eliminated by distillation, diisopropyl ether and ethyl acetate were added to the obtained residue, and obtained

solid was recovered by filtration, drying was carried out and thereby, N-(2-(tert-butoxycarbonyl) aminophenyl)-4-amino benzamide 7.9 g (yield 86 %) were obtained as white solid.

1H NMR (270 MHz, DMSO-d6) delta ppm: 1.46 (9H, s), 5.84 (2H, s), 6.61 (2H, d, J = 8.8 Hz), 7.10-7.18 (2H, m), 7.46-7.55 (2H, m), 7.68 (2H, d, J = 8.8 Hz), 8.67 (1H, s), 9.49 (1H, s).

(0090)

(1-4) .

Into pyridine (7 ml) solution of compound 0.60 g (1.83 mmol) obtained with step (1-3), benzensulphonyl chloride 0.25 ml (2.2 mmol) were gradually added dropwise under ice cooling and next, were stirred for four hours under ice cooling. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with ethyl acetate. Organic layer was washed with 5 % hydrochloric acid aqueous solution, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution and thereafter was dried with sodium sulphate. Desiccant was filtered, and the solvent was eliminated by distillation, diisopropyl ether was added to the obtained residue, and the precipitated solid was recovered by filtration, drying was carried out and thereby, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-benzensulphonyl amino benzamide 0.82 g (yield 95.7 %) were obtained as the pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.42 (9H, s), 7.08-7.24 (5H, m), 7.44-7.66 (4H, m), 7.80-7.85 (4H, m), 8.62 (1H, brs), 9.68 (1H, brs), 10.78 (1H, brs).

(0091)

(1-5) .

4 N hydrochloric acid-dioxane (4 ml) was added at room temperature to the compound 0.30 g (0.64 mmol) obtained with step (1-4) and suspension was made with stirring. It became pale-brown solution several minutes later and further, it became milk-white suspension about 10 minutes later. Further it was stirred for one hour, and thereafter water was added and dissolution was caused, and saturated aqueous sodium bicarbonate was added. It was extracted with ethyl acetate-methyl ethyl ketone and next, organic layer was washed with saturated aqueous sodium chloride solution and was dried with sodium sulphate. After filtration, the solvent was eliminated by distillation, methanol and diisopropyl ether were added to the obtained residue, and precipitated sedimentation was recovered by filtration, drying was carried out and thereby, N-(2-

aminophenyl)-4-benzensulphonyl amino benzamide 0.18 g (yield 76.5 %) were obtained as white solid by drying.

Mp. 216-8 deg C.
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.86 (2H, s), 6.55 (1H, dd, J = 7.3, 8.1 Hz), 6.95 (1H, dd, J = 7.3, 7.3 Hz), 7.10 (1H, d, J = 7.3 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.55-7.64 (3H, m), 7.83-7.86 (4H, m), 9.51 (1H, s), 10.73 (1H, brs).
IR (KBr, cm-1) = 3307 (br), 1634, 1609, 1508, 1456, 1329, 1310, 1290, 1161, 1092, 931, 851.

The compounds from Example 2 to Example 14 were synthesised by the process same as in Example 1. Below melting point (mp.) of the compounds, NMR, data of IR are shown.

(0092)
Example 2.
N-(2-aminophenyl)-4-(N-(2-fluorobenzene) sulphonylamino) benzamide (Table 1, the compound number 6).

Mp. 216-8 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, brs), 6.56 (1H, dd, J = 7.3, 8.1 Hz), 6.74 (1H, d, J = 6.6 Hz), 6.95 (1H, ddd, J = 1.5, 7.3, 8.1 Hz), 7.10 (1H, d, J = 7.3 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.35-7.47 (2H, m), 7.66-7.75 (1H, m), 7.85 (2H, d, J = 8.1 Hz), 7.93 (1H, ddd, J = 1.5, 7.3, 7.3 Hz), 9.50 (1H, brs), 11.0 (1H, brs).
IR (Kbr) cm-1 = 3380, 3319, 1636, 1609, 1509, 1477, 1455, 1167, 938, 852, 757, 745.

(0093)
Example 3.
N-(2-aminophenyl)-4-(N-(2-chlorobenzene sulphonyl) amino) benzamide (Table 1, the compound number 7).

Mp. 213-5 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.84 (2H, brs), 4.56 (1H, dd, J = 8.1, 8.1 Hz), 6.74 (1H, dd, J = 1.5, 8.1 Hz), 6.94 (1H, ddd, J = 1.5, 7.3, 8.1 Hz), 7.09 (1H, d, J = 6.6 Hz), 7.18 (2H,

d, J = 8.8 Hz), 7.50-7.61 (1H, m), 7.83 (2H, d, J = 8.1 Hz), 8.13 (1H, d, J = 7.3 Hz), 9.47 (1H, brs), 11.0 (1H, brs).
IR (KBr) cm-1 = 3358, 1652, 1500, 1453, 1339, 1168, 916, 751.

(0094)
Example 4.
N-(2-aminophenyl)-4-(N-(2-bromobenzene) sulphonylamino) benzamide (Table 1, compound number 8).

Mp. 170 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 7.06-7.27 (5H, m), 7.38-7.44 (1H, m), 7.48-7.72 (2H, m), 7.83 (1H, dd, J = 1.5, 8.1 Hz), 7.93 (2H, d, J = 8.8 Hz), 8.18 (1H, dd, J = 1.5, 8.1 Hz), 10.21 (1H, brs), 11.15 (1H, brs) .
IR (KBr) cm-1 = 3178, 2833, 2567, 1639, 1609, 1541, 1509, 1326, 1237, 1156, 1030, 943.

(0095)
Example 5.
N-(2-aminophenyl)-4-(N-(2-cyanobenzene) sulphonylamino) benzamide (Table 1, compound number 14).

Mp. 205-8 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, brs), 6.57 (1H, dd, J = 8.1, 8.1 Hz), 6.75 (1H, d, J = 8.1 Hz), 6.95 (1H, dd, J = 7.3, 8.1 Hz), 7.10 (1H, d, J = 6.6 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.80-7.95 (4H, m), 8.11 (2H, d, J = 8.8 Hz), 9.52 (1H, s), 11.3 (1H, brs).
IR (Kbr) cm-1 = 3374, 3325(br), 2237, 1635, 1610, 1509, 1455, 1353, 1169, 940, 8 53, 760.

(0096)
Example 6.
N-(2-aminophenyl)-4-(N-(2-trifluoromethyl benzene) sulphonylamino) benzamide (Table 1, compound number 10).

Mp. 153-8 deg C (dec.).

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, s), 6.57 (1H, dd), 6.75 (1H, d) 6.95 (1H, ddd), 7.11 (1H, d), 7.18 (2H, d), 7.80-7.90 (4H, m), 8.01 (1H, dd), 8.14 (1H, d), 9.49 (1H, brs), 11.06 (1H, brs) .
IR (KBr) cm-1 = 3330 (br), 1635, 1508, 1164, 936, 854, 764, 747.

(0097)
Example 7.
N-(2-aminophenyl)-4-(N-(3-chlorobenzene) sulphonylamino) benzamide (Table 1, compound number 22).

Mp. 214-6 deg C.
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.86 (2H, brs), 6.56 (1H, ddd, J = 1.5, 6.6, 7.3 Hz), 6.75 (1H, dd, J = 1.5, 8.1 Hz), 6.95 (1H, ddd, J = 1.5, 7.3, 7.3 Hz), 7.11 (1H, d, J = 6.6 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.62 (1H, dd, J = 8.1, 8.1 Hz), 7.71-7.79 (2H, m), 7.82-7.89 (2H, m), 9.52 (1H, brs), 10.7 (1H, brs).
IR (Kbr) cm-1 = 3375, 3307, 1635, 1608, 1509, 1455, 1166, 934, 853, 676.

(0098)
Example 8.
N-(2-aminophenyl)-4-(N-(2 ,5-dichlorobenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound number 34).

Mp. 182-4 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 7.15-7.3 (5H, m), 7.39-7.42 (1H, m), 7.70 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 2.1, 8.1 Hz), 7.96 (2H, d, J = 8.1 Hz), 8.10 (1H, d, J = 2.8 Hz), 10.23 (1H, brs), 11.30 (1H, brs) .
IR (KBr) cm-1 = 3209, 2822, 1652, 1607, 1559, 1507, 1449, 1235, 1167, 935, 837, 750.

(0099)
Example 9.
N-(2-aminophenyl)-4-(N-(2-nitro-4-methoxybenzene) sulphonylamino) benzamide (Table 1, compound number 41).

Mp. 171-5 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 3.87 (3H, s), 4.86 (2H, brs), 6.57 (1H, dd, J = 7.3, 7.3 Hz), 6.75 (1H, d, J = 7.3 Hz), 6.95 (1H, dd, J = 7.3, 7.3 Hz), 7.11 (1H, d, J = 7.3 Hz), 7.20 (2H, d, J = 7.3 Hz), 7.32 (1H, dd, J = 2.1, 8.1 Hz), 7.59 (1H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.94 (1H, d, J = 2.1 Hz), 9.52 (1H, brs), 10.97 (1H, brs) .
IR (KBr) cm-1 = 3327, 1636, 1607, 1542, 1507, 1457, 1168, 1049.

(0100)
Example 10.
N-(2-aminophenyl)-4-(N-(2,4,6-trimethylbenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound number 42).

Amorphous solid.
1H-NMR (270 MHz, DMSO-d6) delta ppm: 2.23 (3H, s), 2.61 (6H, s), 7.03 (2H, s), 7.09 (2H, d), 7.25-7.51 (4H, m), 7.94 (4H, s), 10.27 (1H, brs), 10.71 (1H, brs) .
IR (KBr) cm-1 = 2853 (br), 1608, 1508, 1456, 1309, 1152, 914, 758, 654.

(0101)
Example 11.
N-(2-aminophenyl)-4-(N-benzylsulphonyl amino) benzamide hydrochloride (Table 1, hydrochloride of compound number 49).

Mp. 158-163 deg C.
1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.59 (2H, s), 7.24-7.38 (10H, m), 7.49-7.52 (1H, m), 8.08 (2H, d, J = 8.8 Hz), 10.32 (1H, brs), 10.37 (1H, brs) .
IR (KBr) cm-1 = 2844 (br), 1634, 1608, 1502, 1152, 929, 904, 757, 699.

(0102)
Example 12.
N-(2-aminophenyl)-4-(N-(2-phenylethyl). sulphonylamino) benzamide (Table 1, compound number 50).
Mp. 227-9 deg C.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 2.95-3.07 (2H, m), 3.4-3.50 (2H, m), 4.88 (2H, brs), 6.59 (1H, dd, J = 6.6, 8.1 Hz), 6.77 (1H, d, J = 8.1 Hz), 6.96 (1H, ddd, J = 1.5, 7.3, 8.1 Hz), 7.12-7.31 (6H, m), 7.33 (2H, d, J = 8.8 Hz), 7.96 (2H, d, J = 8.8 Hz), 9.57 (1H, brs), 10.27 (1H, brs) .
IR (KBr) cm-1 = 3314, 1635, 1510, 1455, 1329, 1144, 934.

(0103)
Example 13.
N-(2-aminophenyl)-4-(N-(pyridine-3-yl) sulphonylamino) benzamide (Table 1, compound 47).
Mp. 235-8 deg C (dec.).

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.86 (2H, brs), 6.57 (1H, ddd, J = 1.3, 7.6, 7.6 Hz), 6.75 (1H, dd, J = 1.3, 7.9 Hz), 6.95 (1H, ddd, J = 1.3, 7.3, 7.9 Hz), 7.10 (1H, d, J = 7.9 Hz), 7.22 (2H, d, J = 8.6 Hz), 7.60-7.66 (1H, m), 7.87 (2H, d, J = 8.9 Hz), 8.17-8.21 (1H, m), 8.80 (1H, d, J = 1.6, 4.9 Hz), 8.96 (1H, d, J = 1.6 Hz), 9.53 (1H, s), 11 (1H, brs).

(0104)
Example 14.
N-(2-aminophenyl)-4-(N-(pyridine-2-yl) sulphonylamino) benzamide (Table 1, compound 46).
Mp. 203-6 deg C.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, brs), 6.56 (1H, dd, J = 7.3, 7.3 Hz), 6.74 (1H, dd, J = 1.5, 8.1 Hz), 6.94 (1H, ddd, J = 1.5, 7.3, 8.1 Hz), 7.10 (1H, d, J = 6.6 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.63-7.69 (1H, m), 7.83 (2H, d, J = 8.8 Hz), 8.03-8.12 (2H, m), 8.71 (1H, d, J = 4.4 Hz), 9,49 (1H, brs), 11.0 (1H, brs).
IR (Kbr) cm-1 = 3354, 3263 (br), 1637, 1609, 1508, 1458, 1348, 1175, 1122, 928.

(0105)
Example 15.
N-(2-aminophenyl)-4-(N-(2-phenoxyethane) sulphonylamino) benzamide (Table 1, compound 54).

1H-NMR (270 MHz, DMSO-d6) delta ppm: 3.67 (2H, t, J = 5.3 Hz), 4.32 (2H, t, J = 5.3 Hz), 4.88 (2H, brs), 6.60 (1H, ddd, J = 1.5, 7.3, 7.6 Hz), 6.76-6.89 (3H, m), 6.92-7.01 (4H, m), 7.15 (1H, d, J = 7.9 Hz), 7.25-7.35 (4H, m), 7.97 (2H, d, J = 8.9 Hz), 9.59 (1H, s), 10.35 (1H, brs).

(0106)

Example 16.

Synthesis of N-(2-aminophenyl)-4-(N-(2-nitrobenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of the compound number 3).

(16-1).

Into pyridine (16 ml) solution of compound 1.06 g (3.24 mmol) obtained with step of Example 1 (1-3), was added 2-nitrobenzene sulphonyl chloride 0.93 g (4.21 mmol) under ice cooling and thereafter while being gradually warmed to room temperature the mixture was stirred for seven hours. Saturated aqueous sodium bicarbonate was added and thereafter extraction was carried out with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the residue obtained by elimination by distillation of the solvent was refined by silica gel column chromatography (chloroform / ethyl acetate = 1:1), and N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(2-nitrobenzene) sulphonylamino) benzamide 1.28 g (yield 77.1 %) were obtained as white solid by further being crystallised from methanol-diisopropyl ether.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.42 (9H, s), 7.11-7.23 (2H, m), 7.25 (2H, d, J = 8.8 Hz), 7.45-7.54 (2H, m), 7.80-7.88 (4H, m), 7.99-8.07 (2H, m), 8.61 (1H, brs), 9.71 (1H, brs), 11.19 (1H, brs).

(0107)

(16-2) .

4 N hydrochloric acid-dioxane (5 ml) was added to methanol (1 ml) suspension of compound 0.20 g (0.39 mmol) obtained with step (16-1) and the mixture was stirred at room temperature for six hours. Diisopropyl ether was added in residue obtained by the elimination of the solvent by distillation, and the obtained residue was recovered by filtration, and drying was carried out, thereby, N-(2-aminophenyl)-4-(N-(2-nitrobenzene) sulphonylamino) benzamide hydrochloride 0.15 g (yield 86 %) were obtained as the pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 7.15-7.29 (5H, m), 7.38 (1H, d, J = 8.1 Hz), 7.82-8.09 (7H, m), 10.19 (1H, brs), 11.26 (1H, brs).
IR (Kbr) cm-1 = 2854 (br), 1652, 1608, 1541, 1506, 1354, 1307, 1164, 934.

(0108)
Example 17.
Synthesis of N-(2-aminophenyl)-4-(N-(3-nitrobenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound 18).

(17-1) .
3-nitrobenzene sulphonyl chloride 0.88 g (3.97 mmol) was added under ice cooling to pyridine (15 ml) solution of compound 1.00 g (3.05 mmol) obtained with step of Example 1 (1-3) and while gradually raising the temperature to room temperature, the mixture was stirred for seven hours. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation of with diisopropyl ether, thereby N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(3-nitrobenzene) sulphonylamino) benzamide 1.37 g (yield 87.6 %) were obtained as the pale pink solid by washing the obtained residue.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.41 (9H, s), 7.09-7.18 (2H, m), 7.25 (2H, d, J = 8.8 Hz), 7.45 (1H, d, J = 7.3 Hz), 7.51 (1H, d, J = 7.3 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.90 (1H, d, J = 7.3 Hz), 8.23 (1H, d, J = 8.1 Hz), 8.48 (1H, dd, J = 2.1, 8.1 Hz), 8.56 (1H, d, J = 2.1 Hz), 8.62 (1H, s), 9.71 (1H, s), 11.0 (1H, brs).

(0109)
(17-2) .
4 N hydrochloric acid-dioxane (5 ml) was added to methanol (1 ml) suspension of compound 0.20 g (0.39 mmol) obtained with step (17-1) and was stirred at room temperature for four hours. Diisopropyl ether was added in residue obtained by the elimination of the solvent by distillation, and obtained residue was recovered by filtration, and, by drying, N-(2-aminophenyl)-4-(N-(3-nitrobenzene) sulphonylamino) benzamide hydrochloride 0.15 g (yield 86 %) were obtained as the pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 7.05-7.34 (6H, m), 7.89 (1H, dd, J = 8.1, 8.1 Hz), 7.94 (2H, d, J = 8.1 Hz), 8.23 (1H, d, J = 8.1 Hz), 8.47 (1H, dd, J = 2.1, 7.3 Hz), 8.57 (1H, d, J = 1.5 Hz), 10.11 (1H, brs), 11.08 (1H, brs) .
IR (KBr) cm-1 = 3386 (br), 3084 (br), 1608, 1532, 1507, 1351, 1168, 1126, 930.

(0110)
Example 18.
4-nitrobenzene sulphonyl chloride 0.88 g (3.97 mmol) were added under ice cooling to pyridine (15 ml) solution of compound 1.00 g (3.05 mmol) obtained with step of synthetic (18-1) Example 1 of N-(2-aminophenyl)-4-(N-(4-nitrobenzene) sulphonylamino) benzamide (Table 1, compound number 26) (1-3) and thereafter the mixture was stirred for four hours while gradually raising the temperature to room temperature. Saturated aqueous sodium bicarbonate was added and thereafter it was extracted with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether was added to the residue obtained by elimination of the solvent by distillation, and obtained solid was recovered by filtration, and N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(4-nitrobenzene) sulphonylamino) benzamide 1.44 g (yield 92 %) were obtained as the straw-coloured solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.41 (9H, s), 7.12-7.23 (2H, m), 7.25 (2H, d), 7.46 (2H, d), 7.51 (2H, d), 7.83 (2H, d), 8.07 (2H, d), 8.40 (2H, d), 8.63 (1H, brs), 9.71 (1H, brs), 11.08 (1H, brs).

(0111)
(18-2) .
To dioxane (5 ml) suspension of compound 0.26 g (0.51 mmol) obtained with step (18-1), was added 4 N hydrochloric acid-dioxane (5 ml) at room temperature and was stirred for three hours. Saturated aqueous sodium bicarbonate was added and neutralisation caused, thereafter it was extracted with ethyl acetate-THF (3:1). Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation, thereby N-(2-aminophenyl)-4-(N-(4-nitrobenzene) sulphonylamino) benzamide 0.20 g (yield 96 %) were obtained as the pale-brown solid by drying the obtained residue.

Mp. 239-41 deg C.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, s), 6.57 (1H, dd, J = 7.3, 7.3 Hz), 6.75 (2H, d, J = 7.3 Hz), 6.95 (1H, dd, J = 7.3, 7.3 Hz), 7.10 (1H, dd, J = 7.3, 7.3 Hz), 7.22 (2H, d, J = 8.8 Hz), 7.87 (2H, d, J = 8.1 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.40 (2H, d, J = 8.8 Hz), 9,54 (1H, brs), 11.03 (1H, brs) .

IR (KBr) cm-1 = 3371, 3310, 1632, 1608, 1529, 1508, 1456, 1349, 1164, 1089, 855, 609.

(0112)

Example 19.

Synthesis of N-(2-aminophenyl)-4-(N-(2-aminobenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of the compound number 2).

(19-1) .

10 % palladium carbon (50 % wet., 0.25 g) was added under a stream of nitrogen into THF (30 ml)-methanol (30 ml) solution of compound 1.00 g (1.95 mmol) obtained with step of Example 16 (16-1), and it was stirred under a stream of hydrogen for one hour. Catalyst was eliminated, thereafter, diisopropyl ether was added to the residue which was obtained by elimination of the solvent by distillation, and precipitated sedimentation was recovered by filtration, and, by drying, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(2-aminobenzene) sulphonylamino) benzamide 0.89 g (yield 95 %) were obtained as white solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.42 (9H, s), 6.05 (2H, s), 6.58 (1H, dd, J = 7.3, 7.3 Hz), 6.76 (1H, d, J = 8.1 Hz), 7.11-7.23 (4H, m), 7.47 (1H, d, J = 8.1 Hz), 7.52 (1H, d, J = 8.8 Hz), 7.59 (1H, d, J = 8.1 Hz), 7.80 (2H, d, J = 8.8 Hz), 8.61 (1H, s), 9.66 (1H, s), 10.72 (1H, brs).

(0113)

(19-2) .

4 N hydrochloric acid-dioxane (5 ml) was added to methanol (1 ml) suspension of compound 0.20 g (0.41 mmol) obtained with step (19-1), and it was stirred for one hour. The solvent was eliminated by distillation, and next obtained residue was washed with diisopropyl ether, and N-(2-aminophenyl)-4-(N-(2-aminobenzene) sulphonylamino) benzamide hydrochloride 0.16 g (yield 85 %) were obtained by drying.

Mp. 210-215 deg C.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 6.58 (1H, dd, J = 7.3, 7.3 Hz), 6.77 (1H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.20-7.53 (5H, m), 7.60 (1H, d, J = 8.1 Hz), 7.97 (2H, d, J = 8.8 Hz), 10.40 (1H, brs), 10.80 (1H, brs) .

IR (KBr) cm-1 = 2835 (br), 1607, 1503, 1476, 1351, 1308, 1169, 1140, 922, 770, 760.

(0114)

Example 20.

Synthesis of N-(2-aminophenyl)-4-(N-(3-aminobenzene) sulphonylamino) benzamide (Table 1, compound number 17)

(20-1)

10 % palladium carbon (50 % wet., 0.30 g) was added under a stream of nitrogen into THF (30 ml)-methanol (30 ml) solution of compound 1.00 g (1.95 mmol) obtained with step of Example 1 7 (17-1) and the mixtrue was stirred under a stream of hydrogen for one hour 30 minutes. Catalyst was eliminated, thereafter, diisopropyl ether was added in the residue which was obtained by elimination of the solvent by distillation, and precipitated sedimentation was recovered by filtration, and, by drying, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(3-aminobenzene) sulphonylamino) benzamide 0.89 g (yield 95 %) were obtained as white solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.42 (9H, s), 5.63 (2H, s), 6.73 (1H, dd, J = 1.5, 8.1 Hz), 6.91 (1H, d, J = 8.8 Hz), 7.03 (1H, d, J = 7.3 Hz), 7.11-7.23 (5H, m), 7.45-7.54 (2H, m), 7.82 (2H, d, J = 8.8 Hz), 8.60 (1H, brs), 9.68 (1H, brs), 10.66 (1H, brs).

(0115)

(20-2).

4 N hydrochloric acid-dioxane (5 ml) was added at room temperature to methanol (2 ml) suspension of compound 0.21 g (0.43 mmol) obtained with step (20-1) and the mixture was stirred for three hours. The residue obtained by elimination of the solvent by distillation was washed with diisopropyl ether, and thereby N-(2-aminophenyl)-4-(N-(3-aminobenzene) sulphonylamino) benzamide hydrochloride 0.16 g (yield 81 %) were obtained as the pale-brown solid by drying.

Mp. >250 degrees.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 6.90-7.51 (10H, m), 7.99 (2H, d), 10.40 (1H, brs), 10.78 (1H, brs) .

IR (KBr) cm-1 = 3420 (br), 2850 (br), 1608, 1507, 1308, 1158, 918.

(0116)

Example 21.

10 % palladium carbon (50 % wet., 0.50 g) was added under a stream of nitrogen to THF (50 ml)-methanol (50 ml) solution of compound 2.20 g (4.3 mmol) obtained with step of synthetic (21-1) Example 18 of N-(2-aminophenyl)-4-(N-(4-aminobenzene) sulphonylamino) benzamide (Table 1, the compound number 25) (18-1), and it was stirred under a stream of hydrogen for one hour at room temperature. Catalyst was filtered, and diisopropyl ether was added to the obtained residue, and, the precipitated solid was recovered by filtration, this solid was refined by silica gel column chromatography (chloroform / methanol / ethyl acetate = 60:3:10), thereby N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(4-aminobenzene) sulphonylamino) benzamide 0.62 g (yield 30 %) were obtained as the pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.42 (9H, s), 6.04 (2H, s), 6.55 (2H, d, J = 8.1 Hz), 7.08-7.20 (4H, m), 7.44-7.53 (4H, m), 7.80 (2H, d, J = 8.1 Hz), 8.62 (1H, brs), 9.66 (1H, brs), 10.36 (1H, brs).

(0117)

(21-2) .

4 N hydrochloric acid-dioxane (10 ml) was added to dioxane (10 ml) solution of compound 0.40 g (0.83 mmol) obtained with step (21-1) and the mixture was stirred at room temperature for five hours. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with ethyl acetate-THF (3:1). Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the residue obtained by elimination by distillation of the solvent was refined by silica gel column chromatography (chloroform / methanol / ethyl acetate = 30:3:10 to chloroform / methanol / water = 6:4:1), and thereby N-(2-aminophenyl)-4-(N-(4-aminobenzene) sulphonylamino) benzamide 0.05 g (yield 16 %) were obtained as the pale-brown amorphous state solid.

Mp. amorphous solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, brs), 6.02 (2H, brs), 6.53-6.65 (3H, m), 6.74 (1H, d), 6.87 (1H, s), 6.95 (1H, dd), 7.09-7.17 (3H, m), 7.45 (2H, d), 7.82 (2H, d), 9.48 (1H, brs), 10.30 (1H, brs).

(0118)

Example 22.

Synthersis of N-(2-aminophenyl)-4-(N-(2-methoxycarbonyl benzene) sulphonylamino) benzamide (Table 1, compound number 13).

(22-1) .

To pyridine (10 ml)-dichloromethane (20 ml) solution of compound 1.00 g (3.05 mmol) obtained with step of Example 1 (1-3), were added under ice cooling 2-chloro sulphonyl benzoic acid methyl ester 0.83 g (6.66 mmol) and the mixture was stirred for five hours while being warmed to room temperature, thereafter it was left to stand overnight. Saturated aqueous sodium bicarbonate was added and thereafter it was extracted with chloroform. Organic layer was washed with hydrochloric acid aqueous solution, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether was added to the residue obtained by elimination of the solvent by distillation, and the precipitated solid was recovered by filtration, and N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(2-methoxycarbonyl benzene) sulphonylamino) benzamide 1.04 g (yield 66 %) were obtained by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.41 (9H, s), 3.89 (3H, s), 7.08-7.23 (4H, m), 7.46 (1H, d, J = 7.3 Hz), 7.46 (1H, d, J = 8.1 Hz), 7.64-7.75 (3H, m), 7.83 (2H, d, J = 8.8 Hz), 7.90-7.96 (1H, m), 8.61 (1H, brs), 9.68 (1H, brs), 10.77 (1H, brs).

(0119)

(22-2) .

4 N hydrochloric acid-dioxane (5 ml) was added to dioxane (3 ml)-methanol (1 ml) suspension of compound 0.30 g obtained with step (22-1) (0.57 mmol) and was stirred at room temperature for four hours. The solvent was eliminated by distillation, and next, saturated aqueous sodium bicarbonate was added, and it was extracted with ethyl acetate. Organic layer was washed with

saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether-methanol was added to the residue obtained by elimination by distillation of the solvent, and formed sedimentation was recovered by filtration, and thereby N-(2-aminophenyl)-4-(N-(2-methoxycarbonyl benzene) sulphonylamino) benzamide 0.13 g (yield 54 %) were obtained by drying.

Mp. 189-92 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 3.88 (3H, s), 4.85 (2H, brs), 6.56 (1H, dd), 6.75 (1H, d), 6.94 (1H, dd), 7.10 (1H, d), 7.18 (2H, d), 7.64-7.74 (3H, m), 7.85 (2H, d), 7.91 (1H, dd), 9.50 (1H, brs), 10.7 (1H, brs) .
IR (KBr) cm-1 = 3274, 1729, 1660, 1506, 1279, 1165, 1119, 762.

(0120)
Example 23.
Synthesis of N-(2-aminophenyl)-4-(N-(2-carboxyl benzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound number 12).

(23-1) .
Lithium hydroxide monohydrate 0.30 g (7.4 mmol) were added to methanol (5 ml)-water (7 ml) suspension of compound 0.64 g (1.22 mmol) obtained with step of Example 22 (22-1) and the mixture was stirred at 50 degrees for five hours. It was allowed to cool, it was acidified with 10 % hydrochloric acid aqueous solution, and thereafter the formed sedimentation was recovered by filtration, and thereby N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(2-carboxyl benzene) sulphonylamino) benzamide 0.56 g (yield 90 %) were obtained as the pale-brown solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.41 (9H, s), 7.1-7.25 (2H, m), 7.24 (2H, d, J = 8.8 Hz), 7.46 (1H, d, J = 8.1 Hz), 7.52 (1H, d, J = 7.3 Hz), 7.60-7.70 (3H, m), 7.80-7.90 (3H, m), 8.60 (1H, brs), 9.69 (1H, brs), 10.53 (1H, brs).

(0121)
(23-2) .

4 N hydrochloric acid-dioxane (4 ml) was added to methanol (4 ml) solution of compound 0.49 g obtained with step (23-1) (0.96 mmol) and was stirred at room temperature for four hours. The solvent was eliminated by distillation, and next, diisopropyl ether was added with obtained residue, and formed sedimentation was recovered by filtration, and N-(2-aminophenyl)-4-(N-(2-carboxyl benzene) sulphonylamino) benzamide hydrochloride 0.24 g (yield 56 %) were obtained by drying.

Mp .> 240 degrees.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 7.2-7.35 (4H, m), 7.35-7.40 (1H, m), 7.45-7.50 (1H, m), 7.60-7.72 (3H, m), 7.90 (1H, d, J = 8.8 Hz), 7.98 (2H, d, J = 8.8 Hz), 10.32 (1H, brs), 10.60 (1H, brs).

IR (Kbr) cm-1 = 3500 (br), 3000-2500 (br), 1698, 1609, 1506, 1389, 1169, 1124, 756.

(0122)

Example 24.

N-(2-aminophenyl)-4-(N-(5-bromo-2-methoxybenzene) sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound 37).

(24-1) .

Into pyridine (8 ml)-dichloromethane (10 ml) solution of compound 0.66 g (2.0 mmol) obtained with step of Example 1 (1-3), 5-bromo-2-methoxybenzene sulphonyl chloride 0.64 g (2.24 mmol) were added under ice cooling and thereafter the mixture was stirred for ten hours while gradually raising temperature to room temperature. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with chloroform. Organic layer was washed with saturated aqueous sodium chloride solution and was dried, and, by washing the residue obtained by elimination of the solvent by distillation with diisopropyl ether, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-(5-bromo-2-methoxybenzene) sulphonylamino) benzamide 0.72 g (yield 62 %) were obtained as pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.41 (9H, s), 3.88 (3H, s), 7.09-7.23 (5H, m), 7.45-7.52 (2H, m), 7.76-7.83 (3H, m), 7.89 (1H, d), 8.63 (1H, brs), 9.66 (1H, brs), 10.66 (1H, brs).

(0123)

(24-2) .

4 N hydrochloric acid-dioxane (5 ml) was added to dioxane (3 ml) suspension of compound 0.19 g obtained with step (24-1) (0.33 mmol) and further methanol (2 ml) was added and was stirred at room temperature for three hours. Diisopropyl ether was added in residue obtained by the elimination of the solvent by distillation, and obtained residue was recovered by filtration, and, by drying, N-(2-aminophenyl)-4-(N-(5-bromo-2-methoxybenzene) sulphonylamino) benzamide hydrochloride 0.15 g (yield 95 %) were obtained as pale-brown solid.

Mp. 181 deg C (dec.).
1H-NMR (270 MHz, DMSO-d6) delta ppm: 3.77 (3H, s), 7.16-7.36 (6H, m), 7.42-7.46 (1H, m), 7.78 (1H, dd), 7.90 (1H, d), 7.96 (2H, d), 10.28 (1H, brs), 10.69 (1H, brs) .
IR (KBr) cm-1 = 3525, 3140 (br), 1613, 1491, 1331, 1277, 1155, 1016, 923, 813, 768.

(0124)
Example 25.
Synthesis of N-(2-aminophenyl)-4-(N-(2-methoxybenzene) sulphonylamino) benzamide (Table 1, the compound number 5)

(24-1)
10 % palladium carbon (50 % wet., 0.24 g) was added under a stream of nitrogen to THF (20 ml)-methanol (10 ml) solution of compound 0.20 g (0.35 mmol) obtained with step (24-1) of Example 24 and the mixture was stirred under a stream of hydrogen for six hours. Catalyst was recovered by filtration, and the filtrate was concentrated, and it was dissolved with dioxane (1 ml) and 4 N hydrochloric acid-dioxane (2 ml) was added and was stirred for two hours and further methanol (2 ml) was added and was stirred for two hours. The solvent was eliminated by distillation, and next saturated aqueous sodium bicarbonate was added, and it was extracted with ethyl acetate-methyl ethyl ketone (2:1). Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether was added to the residue obtained by elimination by distillation of the solvent, and the precipitated solid was recovered by filtration, and N-(2-aminophenyl)-4-(N-(2-methoxybenzene) sulphonylamino) benzamide 0.10 g (yield 72 %) were obtained by drying.

Mp. 213-5 deg C (dec.).

1H-NMR (270 MHz, DMSO-d6) delta ppm: 3.88 (3H, s), 4.84 (2H, brs), 6.56 (1H, dd), 6.74 (1H, d), 6.94 (1H, dd), 7.07 (2H, dd) 7.18 (2+1H, d), 7.58 (1H, dd), 7.81 (2H, d), 7.84 (1H, d), 9.48 (1H, brs), 10.44 (1H, brs) .
IR (KBr) cm-1 = 3340, 3198, 1647, 1605, 1506, 1482, 1320, 1284, 1155, 930, 760.

(0125)
Example 26.
Synthesis of N-(2-aminophenyl)-4-(N-(2-nitrobenzene) sulphonylaminomethyl) benzamide (Table 1, compound number 129).

(26-1) .
To pyridine (20 ml)-THF (20 ml) suspension of methyl 4-aminomethyl benzoate hydrochloride 2.02 g (10.0 mmol), THF (20 ml) solution of 2-nitrobenzene sulphonyl chloride 2.44 g (11.0 mmol) was added under ice cooling dropwise over for 30 minutes, and next, 4-(N,N-dimethylamino) pyridine 0.3 g (2.45 mmol) and triethylamine 5.0 ml (35.6 mmol) were added and the mixture was stirred for six hours while warming gradually to room temperature. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with chloroform. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation, the obtained residue was refined by silica gel column chromatography (chloroform / methanol = 20:1), and thereby methyl 4-(N-(2-nitrobenzene) sulphonylaminomethyl) benzoate 1.90 g (yield 54 %) were obtained as the brown solid.
1H-NMR (270 MHz, CDCl3) delta ppm: 3.89 (3H, s), 4.34 (2H, s), 7.35 (2H, d), 7.50-7.95 (7H, m).

(0126)
(26-2) .
Lithium hydroxide monohydrate 0.36 g (8.48 mmol) were added to methanol (20 ml)-water (17 ml) suspension of compound 1.35 g (3.85 mmol) obtained with step (26-1) and the mixture was stirred at room temperature for eight hours. The sedimentation which remained was recovered by filtration and next, 1 N hydrochloric acid aqueous solution was added to the filtrate, and it was acidified, the obtained precipitate was recovered by filtration, and it was washed with water, and thereby 4-(N-(2-nitrobenzene) sulphonylaminomethyl) benzoic acid 1.20 g (yield 93 %) were obtained as white solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.25 (2H, d), 7.37 (2H, d), 7.74-7.84 (4H, m), 7.94 (2H, d), 8.75 (1H, t), 12.9 (1H, brs).

(0127)

(26-3) .

Thionyl chloride 0.5 ml (6.9 mmol) were added to toluene (15 ml) suspension of compound 0.65 g (2.0 mmol) obtained with step (26-2) and the mixture was stirred at 85 degrees for three hours. The solvent was eliminated by distillation, and next excess thionyl chloride was formed into an azeotrope with toluene. Obtained residue was suspended in dichloromethane (10 ml). Into this solution, was dropwise added under ice cooling pyridine (10 ml)-dichloromethane (5 ml) solution of compound 0.32 g (1.5 mol) obtained with step of Example 1 (1-1). It was stirred for five hours while warming gradually to room temperature, and thereafter it was left to stand overnight. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with chloroform. Organic layer was washed with hydrochloric acid aqueous solution, saturated aqueous sodium chloride solution, and thereafter it was dried, and the residue obtained by elimination by distillation of the solvent was formed into an azeotrope with toluene, and further the obtained residue was washed with diisopropyl ether, and N-(2-(N-tert-butoxycarbonyl amino) phenyl)-4-(N-(2-nitrobenzene) sulphonylaminomethyl) benzamide 0.49 g (yield 65 %) were obtained as the pale-brown solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.45 (9H, s), 4.26 (2H, d), 7.14-7.22 (2H, m), 7.41 (2H, d), 7.51-7.56 (2H, m), 7.78-7.86 (4H, m), 7.93-7.99 (2H, m), 8.68 (1H, brs), 8.76 (1H, t), 9.78 (1H, s).

(0128)

(26-4) .

4 N hydrochloric acid-dioxane (4 ml) was added at room temperature to methanol (2 ml) suspension of compound 0.20 g (0.40 mml) obtained with step (26-3) and the mixture was stirred at room temperature for three hours. The solvent was eliminated by distillation, and next saturated aqueous sodium bicarbonate and ethyl acetate were added to obtained residue, and further it was extracted with ethyl acetate. Organic layer was dried, and the residue from which the solvent was eliminated by distillation, was caused to solidify with methanol-diisopropyl ether, and

thereby N-(2-aminophenyl)-4-(N-(2-nitrobenzene) sulphonylaminomethyl) benzamide 0.14 g (yield 82 %) were obtained as brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.25 (2H, d), 4.89 (2H, brs), 6.60 (1H, dd), 6.78 (1H, d), 6.97 (1H, dd), 7.16 (1H, d), 7.38 (2H, d), 7.78-7.99 (6H, m), 8.75 (1H, d), 9.62 (1H, brs).
IR (Kbr) cm-1 = 3363, 1653, 1540, 1507, 1362, 1339, 1164, 854.

(0129)
Example 27.
Synthesis of N-(2-aminophenyl)-4-(2-(pyridine-3-yl) ethane sulphonylaminomethyl) benzamide (Table 1, compound number 147).

(27-1) .
Triethylamine 42 ml (300 mmol) were added to dichloromethane (450 ml) suspension of 4-aminomethyl benzoic acid 21.16 g (140 mmol). Dichloromethane (50 ml) solution of anhydrous trifluoroacetic acid 60.4 g (287 mmol) was added dropwise while maintaining an internal temperature at 3-8 degrees under ice cooling and next, the mixture was stirred for three hours. Furthermore the reaction liquor was poured into saturated aqueous sodium bicarbonate, thereafter it was acidified with 10 % hydrochloric acid aqueous solution. Precipitated gel state precipitate was recovered by filtration, and, 4-(N-trifluoroacetylamino methyl) benzoic acid 30.4 g (yield 87.8 %) were obtained as milky-white coloured solid by drying.

1H NMR (270 MHz, DMSO-d6) delta ppm: 4.47 (2H, d, J = 5.8 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.93 (2H, d, J = 8.1 Hz), 10.08 (1H, t, J = 5.8 Hz), 12.95 (1H, brs).

(0130)
(27-2) .
Oxalyl chloride 21 g (165 mmol) were gradually added dropwise to dichloromethane (200 ml) suspension of compound 30.0 g (121 mmol) of step (27-1) while being cooled with ice (internal temperature 10-15 degrees). During this, DMF was sometimes added (about 0.1 ml for each 2 ml dropwise addition). After the dropwise addition of the whole quantity, the mixture was stirred till effervescence stopped, and thereafter it was stirred for one hour at 40 degrees. The solvent was eliminated by distillation, and next, excess oxalyl chloride was formed into an azeotrope using

toluene, and thereafter this was dissolved in dichloromethane (100 ml) once again. Into dichloromethane (100 ml)-pyridine (200 ml) solution of compound 22.88 g (110 mmol) of step (1-1), was dropwise added under ice cooling (internal temperature 7-9 degrees) acid chloride solution prepared before.

(0131)

On completion of the dropwise addition it was warmed to room temperature, and next it was left to stand overnight. Saturated aqueous sodium bicarbonate was added to the reaction mixture, and thereafter it was extracted with chloroform, and it was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation. Methanol-diisopropyl ether was added to the obtained residue, and the precipitated solid was recovered by filtration, and, by drying, N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-trifluoroacetylamino methyl) benzamide 28.1 g (yield 58 %) were obtained as the straw-coloured solid.

1H NMR (270 MHz, DMSO-d6) delta ppm: 1.44 (9H, s), 4.48 (2H, d, J = 5.9 Hz), 7.12-7.23 (2H, m), 7.44 (2H, d, J = 8.1 Hz), 7.54 (2H, d, J = 8.1 Hz), 7.94 (2H, d, J = 8.1 Hz), 8.68 (1H, brs), 9.83 (1H, s), 10.10 (1H, br.t, J = 5.9 Hz).

(0132)

(27-3) .

Potassium carbonate 4.70 g (34.0 mmol) were added to methanol (120 ml)-water (180 ml) suspension of compound 13.12 g of step (27-2) (30 mmol), and the mixture was heated to 70 degC for 4 hours with stirring. It was extracted with chloroform, and organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation, and 4-aminomethyl-N-(2-(N-tert-butoxycarbonyl) aminophenyl) benzamide 10.3 g (quantitative) were obtained as the straw-coloured amorphous state solid by drying.

1H NMR (270 MHz, DMSO-d6) delta ppm: 3.80 (2H, s), 7.13-7.23 (2H, m), 7.48-7.58 (4H, m), 7.90 (2H, d, J = 8.1 Hz), 8.69 (1H, brs), 9.77 (1H, brs).

(0133)

(27-4) .

Thionyl chloride 1.6 ml (22 mmol) were added to methanol (65 ml) suspension of 3-pyridine acetic acid hydrochloride 2.29 g (13.2 mmol) and the mixture was heated under reflux for three hours. It was allowed to cool, and thereafter the solvent was eliminated by distillation, and ethyl acetate and saturated aqueous sodium bicarbonate were added to the residue. Furthermore it was extracted with ethyl acetate, and the obtained organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, the solvent was eliminated by distillation and methyl 3-pyridine acetic acid 1.85 g (yield 92.4 %) were obtained as pale-brown oily substance by drying the obtained residue.

1H-NMR (90 MHz, CDCl3) delta ppm: 3.64 (2H, s), 3.72 (3H, s), 7.26 (1H, dd), 7.64 (1H, ddd), 8.50-8.55 (2H, m).

(0134)

(27-5) .

Sodium borohydride 1.15 g (30 mmol) were added under ice cooling to methanol (25 ml) solution of compound 1.85 g (12.2 mmol) obtained with step (27-4) and the mixture was stirred at room temperature for two hours and next heated under reflux for four hours. It was allowed to cool, and the solvent was eliminated by distillation, thereafter water was added to the obtained residue, and furthermore it was extracted with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, the solvent was eliminated by distillation and thereby 2-(pyridine-3-yl) ethanol 1.39 g (yield 92.5 %) were obtained as a straw-coloured oily substance by drying the obtained residue.

1H-NMR (90 MHz, CDCl3) delta ppm: 2.86 (2H, t), 3.88 (2H, t), 7.21 (1H, dd), 7.57 (1H, ddd), 8.32-8.47 (2H, m).

(0135)

(27-6) .

Thionyl chloride 1.14 ml (15.6 mmol) were added into dichloromethane (16 ml) solution of compound 0.88 g (7.1 mmol) obtained with step (27-5) and the mixture was stirred at room temperature overnight. The solvent was eliminated by distillation, and next excess thionyl chloride was formed into an azeotrope with toluene, and diisopropyl ether was added to the

obtained residue, and the precipitated solid was recovered by filtration, and 2-(pyridine-3-yl) ethyl chloride hydrochloride 1.18 g (yield 93 %) were obtained as the pale-brown solid by drying.

1H-NMR (90 MHz, DMSO-d6) delta ppm: 3.30 (2H, t, J = 6.6 Hz), 4.00 (2H, t, J = 6.6 Hz), 8.03 (1H, dd, J = 5.7, 8.1 Hz), 8.55 (1H, ddd, J = 1.5, 1.5, 8.1 Hz), 8.84 (1H, dd, J = 1.5, 5.7 Hz), 8.93 (1H, d, J = 1.5 Hz).

(0136)
(27-7) .
Sodium sulphite 0.93 g (7.4 mmol) were added to water (5 ml) solution of compound 0.66 g (3.7 mmol) obtained with step (27-6) and were heated under reflux at 100 degC for four hours. It was allowed to cool, and thereafter the residue obtained by elimination of the solvent by distillation was applied to reverse phase silica gel chromatography, and fraction eluted with water was concentrated, furthermore it formed into an azeotrope with ethanol and the obtained solid was dried, thereby 2-(pyridine-3-yl) ethanesulphonic acid sodium 0.91 g were obtained as the straw-coloured solid.

1H-NMR (90 MHz, DMSO-d6) delta ppm: 2.64-3.00 (4H, m), 7.28 (1H, dd, J = 4.4, 7.9 Hz), 7.60-7.69 (1H, m), 8.34-8.42 (2H, m).

(0137)
(27-8) .
Thionyl chloride 1 ml was added to compound 0.28 g obtained with step (27-7), and furthermore one drop of DMF was added, and thereafter it was heated at 70 degC for seven hours with stirring. After cooling, the solvent was eliminated by distillation, furthermore excess thionyl chloride was formed into an azeotrope with toluene, thereafter it was suspended in dichloromethane (5 ml). Triethylamine (0.5 ml)-dichloromethane (5 ml) solution of compound 0.5 g (1.46 mmol) obtained with step (26-3) was added under ice cooling, and it was left to stand overnight. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the residue obtained by elimination of the solvent by distillation was refined by silica gel column chromatography (ethyl acetate / methanol 10:1), thereby N-(2-(N-tert-

butoxycarbonyl) aminophenyl)-4-(2-(pyridine-3-yl) ethane sulphonylaminomethyl) benzamide 0.05 g (yield 7 %) were obtained as the pale-brown solid.

1H-NMR (90 MHz, CDCl3) delta ppm: 1.47 (9H, s), 3.0-3.1 (4H, m), 4.3 (2H, d-like), 5.97 (1H, t), 7.1-7.5 (8H, m), 7.6-7.95 (3H, m), 8.25 (1H, s-like), 8.42 (1H, d-like), 9.37 (1H, brs).

(0138)

(27-9) .

Dioxane (2 ml) and methanol (1 ml) were added to the compound 0.05 g obtained with step (27-8), and furthermore 4 N hydrochloric acid-dioxane (2 ml) was added at room temperature and the mixture was stirred at room temperature for two hours. Saturated aqueous sodium bicarbonate was added and thereafter was extracted with ethyl acetate-methyl ethyl ketone (2:1). Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether was added to the residue from which the solvent was eliminated by distillation, and the precipitated solid was recovered by filtration, and N-(2-aminophenyl)-4-(2-(pyridine-3-yl) ethane sulphonylaminomethyl) benzamide 21 mg (yield 50 %) were obtained as the pale-brown solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 2.93-2.99 (2H, m), 3.16-3.33 (2H, m), 4.28 (2H, d, J = 6.3 Hz), 4.90 (2H, s), 6.60 (1H, dd, J = 6.9, 7.3 Hz), 6.79 (1H, d, J = 6.9 Hz), 6.98 (1H, dd, J = 6.9, 7.3 Hz), 7.17 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 4.6, 7.6 Hz), 7.50 (2H, d, J = 8.3 Hz), 7.62 (1H, d, J = 6.9 Hz), 7.87-7.92 (1H, m), 7.98 (2H, d, J = 8.3 Hz), 8.42 (2H, s), 9.67 (1H, s).

(0139)

Example 28.

Synthesis of N-(2-aminophenyl)-4-((pyridine-3-yl) sulphonylaminomethyl) benzamide (Table 1, compound number 145)

(28-1)

Thionyl chloride (5.5 ml)-DMF (0.5 ml) suspension of pyridine-3-sulphonic acid 0.80 g (5.0 mmol) was stirred for four hours while gradually heating under reflux. It was allowed to cool, and thereafter thionyl chloride was eliminated by distillation, and furthermore it was formed into an azeotrope with toluene, and next it was suspended in dichloromethane (20 ml). Triethylamine (2

ml)-dichloromethane (10 ml) solution of compound 1.36 g (4.0 mmol) obtained with step (27-3) was gradually added under ice cooling and the mixture was stirred overnight while being warmed to room temperature. Saturated aqueous sodium bicarbonate was added and thereafter it was extracted with chloroform. Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and the solvent was eliminated by distillation, and the obtained residue was refined by silica gel column chromatography (chloroform / methanol = 30:1 to 10:1), thereby N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-((pyridine-3-yl) sulphonylaminomethyl) benzamide 0.26 g (yield 13.4 %) were obtained as the dark brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.46 (9H, s), 4.18 (2H, s), 7.14-7.23 (2H, m), 7.40 (2H, d, J = 7.9 Hz), 7.52-7.63 (3H, m), 7.87 (2H, d, J = 7.9 Hz), 8.16 (1H, d, J = 7.9 Hz), 8.56 (1H, brs), 8.69 (1H, s), 8.79 (1H, d, J = 4.9 Hz), 8.96 (1H, d, J = 2.3 Hz), 9.81 (1H, brs).

(0140)

(28-2) .

4 N hydrochloric acid-dioxane (2 ml) was added at room temperature into dioxane (2 ml)-methanol (1 ml) solution of compound 0.21 g (0.44 mmol) obtained with step (28-1) and the mixture was stirred at room temperature for two hours. Saturated aqueous sodium bicarbonate was added, thereafter, it was extracted with ethyl acetate-methyl ethyl ketone (2:1). Organic layer was washed with saturated aqueous sodium chloride solution, and thereafter it was dried, and diisopropyl ether was added to the residue obtained by elimination of the solvent by distillation, and the precipitated solid was recovered by filtration, and N-(2-aminophenyl)-4-((pyridine-3-yl) sulphonylaminomethyl) benzamide 93 mg (yield 55 %) were obtained as the brown solid by drying.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 4.15 (2H, d, J = 5.9 Hz), 4.87 (2H, s), 6.60 (1H, dd, J = 7.3, 7.6 Hz), 6.78 (1H, dd, J = 1.3, 8.3 Hz), 6.97 (1H, ddd, 1.3, 7.3, 7.9 Hz), 7.16 (1H, d, 6.9 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.61 (1H, dd, J = 4.9, 7.9 Hz), 7.90 (2H, d, J = 8.3 Hz), 8.17 (1H, ddd, J = 1.3, 1.5, 8.1 Hz), 8.52 (1H, t, J = 5.9 Hz), 8.80 (1H, dd, J = 1.5, 4.6 Hz), 8.95 (1H, d, J = 1.5 Hz), 9.63 (1H, s).

(0141)

Example 29.

Synthesis of N-(2-aminophenyl)-4-(N-methyl-N-{3-(N, synthesis of N-dimethylamino) benzene} sulphonylamino) benzamide hydrochloride (Table 1, hydrochloride of compound 45).

(29-1) .
Potassium carbonate 0.68 g (4.92 mmol) were added to acetone (10 ml) solution of compound 0.40 g (0.83 mmol) obtained with step (20-1) of Example 20, and methyl iodide (0.3 ml, 4.9 mmol) was added, and it was heated under reflux for one hour and thereafter allowed to cool, the same amount of methyl iodide was added once again and was heated under reflux for one hour. The solvent was eliminated by distillation, and next obtained residue was refined by silica gel column chromatography (chloroform / ethyl acetate = 5:1), and N-(2-(N-tert-butoxycarbonyl) aminophenyl)-4-(N-methyl-N-{3-(N,N-dimethylamino) benzensulphonyl} amino) benzamide 0.12 g (yield 28 %) were obtained as the pale-brown solid.

1H-NMR (270 MHz, DMSO-d6) delta ppm: 1.44 (9H, s), 2.87 (6H, s), 3.18 (3H, s), 6.62 (1H, s), 6.76 (1H, d), 6.99 (1H, d), 7.12-7.23 (2H, m), 7.31-7.39 (3H, m), 7.50-7.56 (2H, m), 7.92 (2H, d), 8.66 (1H, brs), 9.84 (1H, brs).

(0142)
(29-2) .
4 N hydrochloric acid-dioxane (5 ml) was added to dioxane (3 ml)-methanol (2 ml) solution of compound 0.08 g (0.15 mmol) obtained with step (29-1) and the mixture was stirred at room temperature for four hours. The solvent was eliminated by distillation, and next it was washed with diisopropyl ether, and thereby N-(2-aminophenyl)-4-(N-methyl-N-{3-(N,N-dimethylamino) benzensulphonyl} amino) benzamide hydrochloride 0.06 g (yield 87 %) were obtained as the pale-brown solid.

Amorphous solid.
1H-NMR (270 MHz, DMSO-d6) delta ppm: 2.90 (6H, s), 3.20 (3H, s), 6.70 (1H, s), 6.76 (1H, d, J = 8.1 Hz), 7.01 (1H, dd, J = 2.1, 8.1 Hz), 7.32-7.50 (7H, m), 7.55 (1H, d, J = 6.6 Hz), 8.08 (2H, d, J = 8.1 Hz), 10.57 (1H, brs) .
IR (KBr) cm-1 = 3367, 2858, 1607, 1497, 1346, 1177, 870, 760.

(0143)